University of Chester

The effects of exercise on body mass and body composition in postmenopausal breast cancer survivors: a systematic review.

"Dissertation submitted in accordance with the requirements of the University of Chester for the degree of Master of Science."

Sarah Hart

September 2012

Acknowledgements

I would like to acknowledge and thank Dr Steven Fallows for his help and guidance during the preparation of this systematic review.

The effects of exercise on body mass and body composition in postmenopausal breast cancer survivors: a systematic review.

Abstract

Purpose: The aim of this systematic review was to determine the effects of exercise on the body mass (BM), body mass index (BMI), waist circumference (WC), lean body mass (LBM), fat mass (FM), body fat percentage (BF%), bone mineral content (BMC) and bone mineral density (BMD) of postmenopausal breast cancer survivors (BCSs).

Method: Records were located via; electronic searches of MEDLINE, Cochrane Library, CINAHL, ProQuest, Sport Discus, PEDro, ZETOC and SCIRUS and handsearches of key journals and book chapters. All searches covered the period from the start of 1989 to the end of June 2012. All identified records were screened against predetermined eligibility criteria. Records that met the full eligibility criteria were included in the final review, and assessed for methodological quality using the Downs and Black Checklist (1998).

Results: A total of 5714 records (excluding duplicates) were located; five studies and six groups of exercising postmenopausal BCSs were included in the final review. The differences in the mean change between exercising and control postmenopausal BCSs ranged from 0.70kg to -2.42kg for BM; -0.28kg/m^2 to -0.86kg/m^2 for BMI; -0.54cm to -3.00cm for WC; 0.1kg to 1.0kg for LBM; 0.5kg to -2.0kg for FM; 0.2% to -2.0% for BF%; -46g/cm to 68g/cm for BMC; 0.000g/cm^2 to 0.033g/cm^2 for total BMD and 0.004g/cm^2 to 0.260g/cm^2 for lumbar spine BMD.

Conclusion: The findings from individual studies were mixed, however overall exercise had a small favourable effect on the body composition of

postmenopausal BCSs (↓BM, ↓BMI, ↓WC, ↑LBM, ↓FM, ↓BF%, ↑BMC and ↑BMD). Further research into the effects of combined aerobic and resistance exercise over longer total exercise durations of 6 to 12 months are warranted. Future studies should include larger sample sizes so that results can be stratified by important confounding factors, without statistical power being compromised.

Keywords: physical activity; body weight; body fat; lean body mass; mammary neoplasm; recovery

Declaration

"This work is original and has not been submitted previously in support of a degree qualification or other course."

Signed:

Dated:

Table of contents

List of Contents \cont.

Table of contents \cont.

Table of contents \cont.

List of Tables

List of Figures

List of Appendices

Table of abbreviations

Abbreviation	Full title
ACSM	American College of Sports Medicine
ADP	Air displacement plethysmography
AO(s)	Anti oestrogen(s)
AI(s)	Aromatase Inhibitor(s)
AT	After Treatment
BCS(s)	Breast cancer survivor(s)
BF%	Body fat percentage
BIA	bioelectric impedance
BM	Body mass
BMI	Body mass index
BMC	Bone mineral content
BMD	Bone mineral density
CCRBT	Cochrane Collaboration Risk of Bias Tool
CBT	Cognitive behavioural therapy
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
CT	Chemotherapy Treatment
CVD	Cardiovascular disease
DEXA	dual-energy-X-ray-absorptiometry
EB	Energy balance
EE	Energy expenditure
EI	Energy intake
FFM	Fat free mass
FM	Fat mass
HM	Home based
HR(s)	Hazard ratio(s)
HQTS	High Quality Training Study
LBM	Lean body mass
MESH	Medical Subject Headings
MRI	Magnetic resonance imaging

Table of abbreviations /cont.

abbreviation	Full title
PA	Physical activity
PACC	Physical Activity and Cancer Control
PEDro	Physiotherapy Evidence Database
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT(s)	Randomised control trial(s)
REE	Resting energy expenditure
RF	Recreational Fitness
RR	Relative risk
RT	Radiotherapy treatment
S	Supervised
SHBG	Sex Hormone Binding Globulin
SKF(s)	Skin fold(s)
SMD	Standard mean difference
SUR	Surgery
UNV	University
UNS	Unsupervised
WC	Waist circumference
WMD	Weighted mean differnce
WMES(s)	Weighted mean effect size(s)
95%CI(s)	95% confidence interval(s)

The effects of exercise on body mass and body composition in postmenopausal breast cancer survivors: a systematic review.

1.0. Rationale

1.1. Rationale for conducting a systematic review on the effects of exercise on the body mass and body composition of postmenopausal breast cancer survivors

It was estimated that in 2008 there were 5.5 million breast cancer survivors (BCSs) alive worldwide (Boyle & Levin, 2008). The vast majority of BCSs are postmenopausal at diagnosis (Cancer Research UK, 2011a; Key, Verkasalo, & Banks, 2001).

Overweight and obesity increase the risk of postmenopausal breast cancer and reduce the risk of premenopausal breast cancer (Cancer Research UK, 2011a). However, during treatment and recovery, premenopausal BCSs gain a greater amount of body mass (BM) and experience greater adverse body composition changes than postmenopausal BCSs (Vance, Mourtzakis, McCargar, & Hanning, 2011). Therefore the findings from exercise and body composition research that includes BCS populations with mixed menopausal statuses may not be representative of either group and important effects may be disguised.

Postmenopausal BCSs gain a greater than expected amount of BM during treatment and recovery, and this may be of an atypical sarcopenic type (Vance et al., 2011). Sarcopenic BM gain is characterised by increased fat mass (FM) and decreased lean body mass (LBM) (Heber et al., 1996). In addition, some treatments for postmenopausal breast cancer can result in reductions in bone mineral content (BMC) and bone mineral density (BMD) (Chien & Goss, 2006). These adverse body composition changes have been associated with an

increased risk of adverse outcome (Bradshaw et al., 2012; Chen et al., 2009; Kroenke, Chen, Rosner, & Holmes, 2005; Nichols et al., 2009).

Exercise may help overcome some of these adverse body composition changes and it has been widely reported that exercise is both safe and beneficial for BCSs (A. Campbell, Stevinson, & Crank, 2011; Hayes, Spence, Galvão, & Newton, 2009; Macmillan Cancer Support, 2011; Schmitz et al., 2010). However there is a lack of studies specifically addressing the effects of exercise in older postmenopausal BCSs (Visovsky, 2006). The effects of specific exercise prescriptions on the BM and body composition of postmenopausal BCSs are not known (Schmitz et al., 2010).

A systematic review can summarise what is known about a particular intervention so as to resolve conflicting evidence or to confirm current practice (Centre for Reviews and Dissemination, 2009, p. v; Green & Higgins, 2011). A systematic review can also demonstrate where knowledge is lacking, so as to highlight areas that require further research (Centre for Reviews and Dissemination, 2009, p. v; Green & Higgins, 2011). Therefore the aim of this systematic review was to determine the effects of exercise on the BM, body mass index (BMI), waist circumference (WC), LBM, FM, body fat percentage (BF%), BMD and BMC of postmenopausal BCSs.

For full definitions of terms, refer to the glossary attached in Appendix 1.

2.0. Introduction

2.1. Breast cancer incidence, survival and prevalence

Breast cancer is the most common female cancer in the world, in 2008 it was estimated that 1.38 million women were diagnosed with breast cancer (Ferlay et al., 2010). The lifetime risk of a woman in the UK developing breast cancer is 1:8; however the risk is strongly related to age and increases to 1:13 at age 69 (Table 1) (Cancer Research UK, 2012).

Table 1

Estimated risk of developing breast cancer by age among women in the UK in 2008

Age	Estimated risk of breast cancer
29	**1 in 2000**
39	**1 in 215**
49	**1 in 50**
59	**1 in 22**
69	**1 in 13**
Lifetime risk	**1 in 8**

(Adapted from Cancer Research UK, 2012)

The average age of the menopause is 50 years (Key, Verkasalo, et al., 2001). As 80% of breast cancer cases occur in women aged >50 years the vast majority of cases occur in postmenopausal women (Cancer Research UK, 2011a).

The incidence of breast cancer in the UK has increased from 23,876 in 1978 to 46,537 in 2008; a 65% increase in the age-standardised incidence rate (ASIR)

(Cancer Research UK, 2011a). Due to an expanding population, with an increasing proportion of elderly persons, the incidence of breast cancer has been predicted to increase by 26% between 2007 and 2030 (Mistry, Parkin, Ahmad, & Sasieni, 2011).

Advances in detection and improvements in treatment have resulted in improved prognoses for women with breast cancer (Bray, McCarron, & Parkin, 2004). Age-standardised five year survival rates in England and Wales have increased from 52% in 1975 to 82% in 2006 (Fig.1) (Cancer Research UK, 2009). The predicted twenty-year survival rate for breast cancer patients diagnosed in 2001-2003 was 64% (Cancer Research UK, 2009).

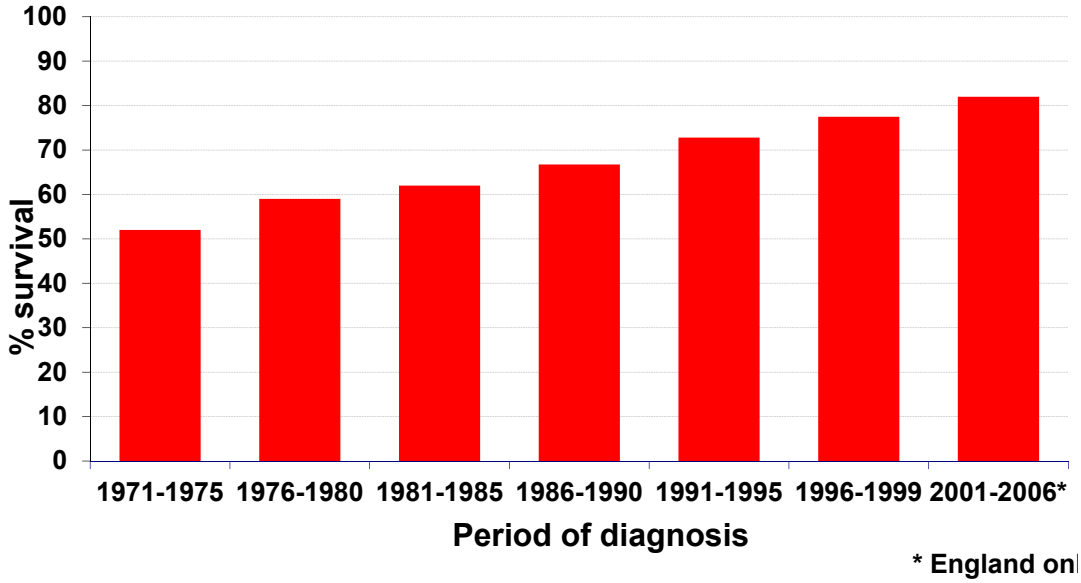

Figure 1

Age-standardised five-year relative survival rate, female breast cancer, England and Wales, 1971-2006 (Adapted from Cancer Research UK, 2009)

A cancer survivor is anyone who has been diagnosed with cancer, from the point of diagnosis up until the end of their life and includes all people who have recovered (J. K. Brown et al., 2003). Increased incidence and improved prognoses have created an expanding population of BCSs. It was estimated that in 2008 there were 5.5 million BCSs alive worldwide (Boyle & Levin, 2008). Compared to other common cancers breast cancer has a proportionally high incidence and proportionally low mortality (Maddams, Møller, & Devane, 2008). In 2004 28% of all cancer survivors in the UK were BCSs, making them the most prevalent group (Fig.2) (Maddams et al., 2008).

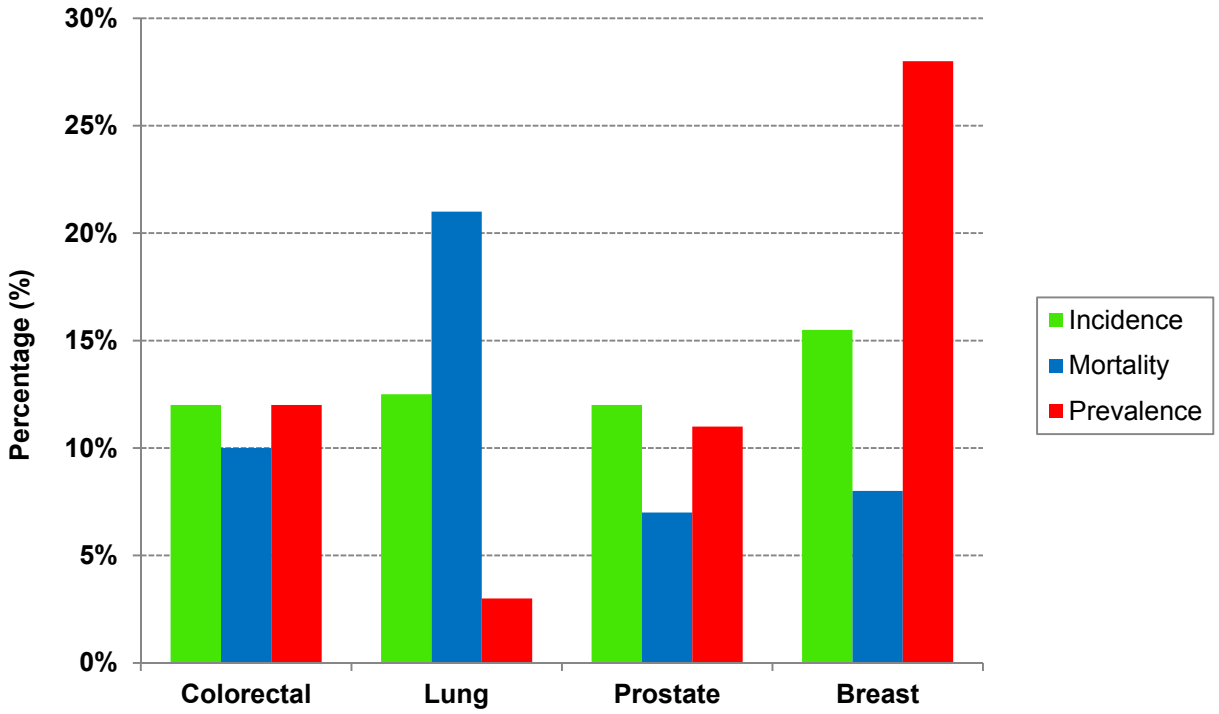

Figure 2

Proportion of total incidence, mortality and prevalence contributed by each of the four major cancers in England, 2004 (Adapted from Maddams et al., 2008)

Even if current survival rates are maintained, the predicted increase in incidence means that the numbers of postmenopausal BCSs are predicted to increase dramatically. Therefore the health, well-being and long term care of postmenopausal BCSs is set to become an increasing challenge which will be of considerable importance to researchers, healthcare providers and policy makers.

2.2. Stages in the cancer experience

The Physical Activity and Cancer Control (PACC) Framework indentifies six stages in the cancer experience; two pre-diagnosis stages; pre-screening and screening and four post-diagnosis stages; pre-treatment, treatment, survivorship and end of life (Fig.3) (Courneya & Friedenreich, 2007).

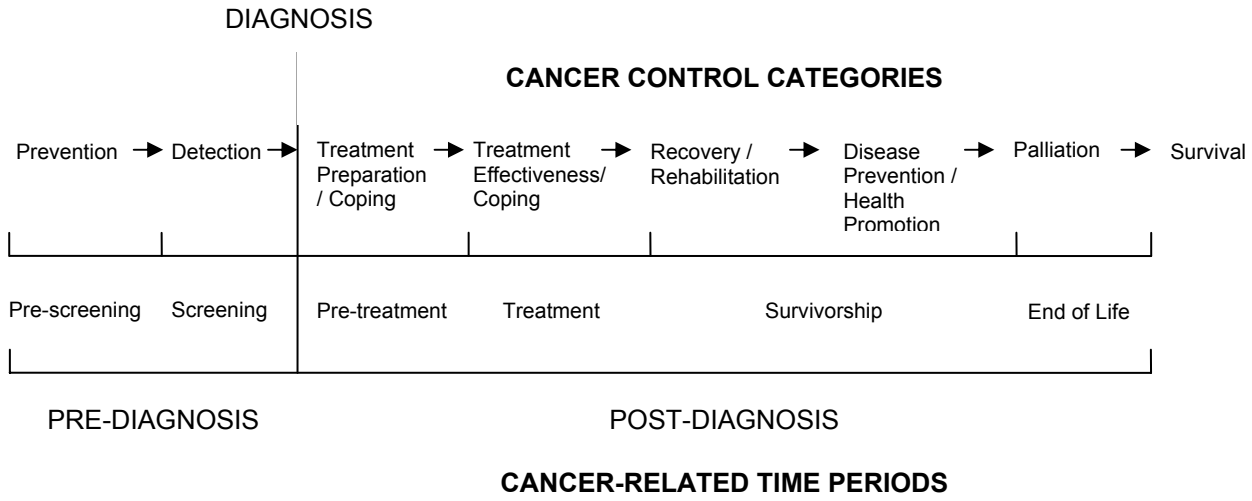

Figure 3

Physical Activity and Cancer Control Framework

(Adapted from Courneya & Friedenreich, 2007)

The PACC framework improves communication and enables health care professionals and researchers to clearly and effectively target specific stages of the cancer experience.

2.3. Types and stages of breast cancer

There are several different types of breast cancer. Breast cancers are staged using the Tumour, Node, Metastasis (TNM) or the number system of breast cancer staging. For readers unfamiliar with the different types of breast cancer or the staging systems summaries are provided in Appendices 2, 3 and 4 respectively.

2.4. The aetiology of breast cancer

The aetiology of breast cancer is complex and multi faceted however, many of the risk factors are linked to lifetime exposure to oestrogens (Key, Verkasalo, et al., 2001). Oestrogens are thought to increase breast cancer risk by increasing the proliferation, and inhibiting the apoptosis, of mammary cells (Boyle & Levin, 2008, pp. 140-141). This increases the likelihood of mutations occurring and being replicated; it is the replication of mutations in mammary cells that leads to the development of breast cancer (Key, Allen, Verkasalo, & Banks, 2001).

In premenopausal women the major source of oestrogens is the ovaries (Key, Allen, et al., 2001). The menopause is marked by the ending of menstruation; once menstruation has ceased for twelve months a woman is postmenopausal. In postmenopausal women the ovaries no longer produce oestrogens and the major source of oestrogens is from the aromatisation of androgens in adipose tissue (Key, Allen, et al., 2001).

BMI is a measure of mass relative to height and BMI is often used to determine overweight and obesity (World Health Organisation, 2004). A BMI of 18.5kg/m^2, 18.6-24.9kg/m^2, 25-29.9kg/m^2 and >30kg/m^2 indicates underweight, healthy weight, overweight and obese respectively (World Health Organisation, 2004). There is clear and consistent evidence that overweight and obesity increase the risk of postmenopausal breast cancer and reduce the risk of premenopausal breast cancer (Bergstrom, Pisani, Tenet, Wolk, & Adami, 2001; Bianchini, Kaaks, & Vainio, 2002; Lahmann et al., 2004; Reeves et al., 2007; Renehan, Tyson, Egger, Heller, & Zwahlen, 2008).

Compared to premenopausal women of a healthy weight (BMI 22.5-24.9kg/m^2) obese premenopausal women (BMI >30kg/m^2) have a 20% reduction in breast cancer risk (Cancer Research UK, 2012). Compared to postmenopausal women of a healthy weight (BMI 22.5-24.9 kg/m^2), moderately overweight (BMI 25-27.4kg/m^2), overweight (BMI 27.5-29.5 kg/m^2) and obese (BMI >30kg/m^2) postmenopausal women have a 10%, 20% and 30% increased risk of breast cancer respectively (Cancer Research UK, 2012).

Overweight and obesity are thought to reduce the risk of premenopausal breast cancer by increasing the number of anovulatory menstrual cycles, and therefore reducing exposure to oestrogens (Key, Allen, et al., 2001). Overweight and obesity are thought to increase the risk of postmenopausal breast cancer by increasing the production of oestrogens from the aromatisation of androgens in adipose tissue (Key, Allen, et al., 2001). In addition sex hormone-binding globulin (SHBG), which binds to oestrogens and determines the concentration of free serum oestrogens, falls with increasing

BMI, resulting in increased levels of free serum oestrogens (Key, Allen, et al., 2001).

Given the greater prevalence of postmenopausal breast cancer, and given the differing roles of overweight and obesity in the aetiology of premenopausal and postmenopausal breast cancer, the remainder of this dissertation will focus on postmenopausal BCSs.

2.5. Treatments for breast cancer and their side effects

Treatments for postmenopausal breast cancer have the potential to cause a wide range of short and long term side effects (Schmitz et al., 2010). These side effects include increases in BM and reductions in BMD. For readers unfamiliar with breast cancer treatments and their side effects a summary is provided in Appendix 5.

2.6. BM gain in postmenopausal BCSs during the treatment stage of the breast cancer experience

Significant gains in BM can occur during the treatment stage of the breast cancer experience (Chlebowski, Aiello, & McTiernan, 2002; Demark-Wahnefried, Rimer, & Winer, 1997; Vance et al., 2011). In healthy women the menopause has been associated with BM gains of 0.54kg/yr (Guo, Zeller, Chumlea, & Siervogel, 1999) and 0.47kg/yr (Wing, Matthews, Kuller, Meilahn, & Plantinga, 1991); greater gains of 1.1kg/yr have been observed among users of hormone replacement therapy (Wing et al., 1991).

However during 6 months of chemotherapy treatment postmenopausal BCSs gained a mean of 2.8kg and gains of up to 5.5kg were reported (Del Rio et al.,

2002). Among BCSs with a age mean of 55.5 years Genton, Kyle, Balmer Majno, and Pichard (2006) reported a mean BM gain of 2.2kg (±3.1kg) during primary treatment and an additional mean gain of 0.6kg (±1.2kg) during radiotherapy. The mean BM gains among BCSs reported by Del Rio et al. (2002) and Genton et al. (2006) were in excess of those reported among healthy postmenopausal women.

2.7. BM gain in postmenopausal BCSs during the recovery and survivorship stages of the breast cancer experience

Significant gains in BM are a progressive and persistent problem among BCSs (Vance et al., 2011). However premenopausal BCSs gain significantly more BM than postmenopausal BCSs, during the recovery and survivorship stages of the breast cancer experience (Freedman et al., 2004; Goodwin et al., 1999; Makari-Judson, Judson, & Mertens, 2007; Tredan et al., 2010). Nevertheless, Goodwin et al. (1999) and Tredan et al. (2010) reported respective mean BM gains of 1.05kg (95%CI, 0.5 to 1.6kg) and 1.0kg (±4.3kg) among postmenopausal BCSs, one year after the commencement of treatment. In the Tredan et al. (2010) study, 14% of postmenopausal BCSs gained 5% to 10% of their baseline BM, and 7% gained >10% of their baseline BM.

Evidence from studies with longer follow-up periods suggests that BM gain among postmenopausal BCSs is persistent. After a median follow-up of 3.1 years, Heideman, Russell, Gundy, Rookus, and Voskuil (2009) observed a mean increase in BM of 1.1kg (±.5.0kg) among postmenopausal BCSs; 31.9% had gained 2kg to 4kg and a further 17.6% had gained >5kg. Makari-Judson et al. (2007) reported that, one year from diagnosis, postmenopausal BCSs had

gained 0.8kg (±0.4kg); two years from diagnosis this had increased to 1.3kg. Saquib et al. (2007) reported that only 10% of BCSs who gained >5% of their pre-diagnosis BM, returned to their pre-cancer BM during six years of follow-up. Data relating to the impact of chemotherapy on BM gain in specific postmenopausal BCS samples is lacking. However, although individual data was not presented, Irwin, McTiernan, Baumgartner, et al. (2005) observed a greater BM gain among postmenopausal BCSs who received chemotherapy, than those who did not. Studies of mixed premenopausal and postmenopausal BCSs have consistently reported that BCSs who receive chemotherapy gain significantly more BM than those who do not (Goodwin et al., 1999; Heideman et al., 2009; Makari-Judson et al., 2007; Saquib et al., 2007). Therefore it is possible that chemotherapy may be associated with greater BM gain in postmenopausal BCSs.

The estimation of BM gain among postmenopausal BCSs is challenging, as this population is heterogenic, and includes a wide range of; ages, ethnicities, BMIs, types of breast cancer, stages of breast cancer, treatment regimes and stages of treatment. In addition studies may vary by design, sample selection, follow-up periods and definitions of significant BM gain and this makes comparisons between studies difficult (Vance et al., 2011).

Nevertheless, the evidence suggests that BM gain among postmenopausal BCSs is greater than would be expected among healthy women and is a progressive and persistent problem throughout the treatment, recovery and survivorship stages of the cancer experience.

2.8. Methods of body composition assessment in postmenopausal BCSs

BMI is frequently used to assess overweight and obesity and is a measure of mass relative to height (World Health Organisation, 2004). However, the isolated use of BMI is limited when determining body composition, as BMI does not distinguish between FM and LBM, and has a poor sensitivity to detect excess adiposity (Cornier et al., 2011). Both the total amount, and the distribution of FM, are important when determining the risk of obesity related co-morbidities as intra-abdominal fat is associated with a greater risk (Alberti, Zimmet, & Shaw, 2006). WC may be better able to predict intra-abdominal fat mass than BMI (Klein et al., 2007). Therefore the combined use of BMI and WC has been recommended to assess obesity, due to the simplicity and high reproducibility of the method (National Institute for Health and Clinical Excellence, 2006, pp. 198-199; World Health Organisation, 2004). In women the risk of obesity related co-morbidities starts to increase when WC is >80cm, and significantly increases when WC is >88cm (Alberti et al., 2006; National Institute for Health and Clinical Excellence, 2006; World Health Organisation, 2004).

When determining body composition it is necessary to distinguish between FM, FFM, LBM, BF%, BMD and BMC (Table 2) (Heyward & Wagner, 2004, p. 5). It is not possible to directly determine body composition in living individuals, however a range of indirect methods are available, including; anthropometry (including circumference measurements and skinfolds [SKF]), hydrostatic weighing, air displacement plethysmography (ADP), dual-energy-X-ray-absorptiometry (DEXA), computed tomography/magnetic resonance imaging

(MRI) and bioelectric impedance (BIA) (Cornier et al., 2011; Heyward & Wagner, 2004).

Table 2

Definitions of commonly used body composition terminology

Term	Abbreviation	Definition
Body Mass	**BM**	The size of the body. Commonly referred to as body weight.
Body Mass Index	**BMI**	A measure of mass relative to height.
Fat mass	**FM**	The absolute amount of body fat; includes all extractable lipids from adipose tissue and all other tissues in the body.
Fat free mass	**FFM**	All residual lipid-free tissues and chemicals the body including; water, muscle, bone, connective tissue and internal organs.
Lean body mass	**LBM**	Is similar to, but distinct from, FFM. LBM is FFM plus a small amount of essential lipids.
Essential lipids		Phospholipids required for cell membrane function.
Body fat percentage **Percentage body fat**	**BF%** **%BF**	Levels of FM expressed as a percentage of the total body mass. %BF = FM/BM x 100. The terms BF% and %BF are interchangeable.
Bone Mineral Content	**BMC**	The absolute amount of bone mineral content.
Bone Mineral Density	**BMD**	The amount of bone mineral content expressed relative to the cross sectional area of the bone.

(Adapted from Heyward & Wagner, 2004)

DEXA has been shown to be valid and reliable and is considered to be one of the reference methods for body composition analysis (Heyward & Wagner, 2004, pp. 40-44). However, body composition assessment methods that are

valid in the general population may not be valid in BCS populations (Battaglini et al., 2011; Freedman et al., 2004). BIA has been shown to overestimate BF% compared to three-site SKF, seven-site SKF, and ADP in a small sample of 14 BCSs with mixed menopausal statuses (Battaglini et al., 2011). Freedman et al. (2004) used; ADP, BIA and DEXA to assess body composition change among a small sample of 20 BCSs (50% postmenopausal). In this study ADP, as opposed to BIA, was shown to overestimate BF%, and mean increases in BF% were estimated to be 4.1% by ADP, 0.6% by BIA and 0.9% by DEXA (Freedman et al., 2004). Therefore it is important to consider the strengths, weaknesses, limitations, validity and reliability of the methods used to assess body composition in BCS populations.

2.9. Body composition change in postmenopausal BCSs during the treatment and survivorship stages of the breast cancer experience

In healthy women BM gain typically includes an increase in both FM and LBM and, on average, LBM accounts for 38% of BM gain (Forbes, Brown, Welle, & Lipinski, 1986). In contrast when BCSs gain BM it occurs without the associated gains, or even losses in LBM; this is referred to as sarcopenic BM gain or sarcopenic obesity (Heber et al., 1996; Vance et al., 2011). Although Del Rio et al. (2002) and Genton et al. (2006) reported a typical pattern of BM gain in postmenopausal BCSs, sarcopenic BM gains have been reported by Cheney, Mahloch, and Freeny (1997); Harvie, Howell, Thatcher, Baildam, and Campbell (2005) and Irwin, McTiernan, Baumgartner, et al. (2005).

In a small study Cheney et al. (1997) reported that, during treatment, three postmenopausal BCSs lost a mean BM of 1.1kg, and five BCSs (three

postmenopausal and two premenopausal) gained a mean BM of 3.3kg. Among those who gained BM, FM increased by a mean 4.4kg whilst LBM declined by 1.3kg (Cheney et al., 1997). Two of the postmenopausal BCSs who lost BM also experienced increases in FM and reductions in LBM (Cheney et al., 1997). Harvie et al. (2005) observed sarcopenic BM gains in BCSs with a mean age of 55.9 years (±.6.5yrs) during chemotherapy treatment; FM increased by 1.5kg (95%CI; -1.2 to 4.4kg) and FFM declined by -1.9kg (95%CI; -4.9 to 1.1kg), this led to a 2.1% increase in BF% (95%CI; 0.8 to 3.5%; p=<0.05). Irwin, McTiernan, Baumgartner, et al. (2005) reported that between the first to third year post-diagnosis, 74% of BCSs (69% postmenopausal) experienced increases in BF%; among these BF% gainers the mean increase was 3.6% (±.3.0%). Increases in BF% ranged from 0.1% to 15.0% and some BCSs experienced increases in BF% without associated BM gains (Irwin, McTiernan, Baumgartner, et al., 2005). These findings suggest that adverse body composition change can occur even among BCSs who lose BM. Therefore body composition assessments must be made alongside measures of BM in postmenopausal BCSs.

Serum oestrogen levels are important for the maintenance of BMC and BMD. Some treatments for postmenopausal breast cancer, such as aromatase inhibitors (AIs), can result in lowered BMC and BMD (Irwin, Alvarez-Reeves, et al., 2009). In healthy women oestrogens decline after the menopause and bone loss occurs at 1% a year; however a greater and more abrupt reduction in oestrogens occurs in postmenopausal BCSs who are prescribed AIs; as a result bone loss can occur at an accelerated rate of 2.6% a year (Chien & Goss, 2006).

The number of studies assessing body composition change in postmenopausal BCSs is limited. However, it appears that postmenopausal BCSs can experience greater than normal reductions in BMD and can develop an atypical, sarcopenic, pattern of body composition change which can occur with or without associated BM gain.

2.10. Adverse effects of overweight and obesity among postmenopausal BCSs

Many postmenopausal BCSs have additional obesity related co-morbidities at diagnosis; one study reported that 25% to 50% had hypertension, 15% to 27% had coronary heart disease, and 5% to 10% had type II diabetes (Yancik et al., 2001). Compared to the age and sex-specific mortality rate of the general population, BCSs had an increased risk of non cancer death (Hazard Ratio [HR] 1.09); this was attributed to the side effects of treatments and the effects of co-morbidities (B. W. Brown, Brauner, & Minnotte, 1993).

Compared to BCSs of a healthy weight, obese BCSs had an increased risk of all-cause mortality (HR 1.31; [95%CI; 1.12 to 1.54]) (Dignam et al., 2003). Compared to BCSs without type II diabetes, those with pre-existing type II diabetes had an increased risk of all-cause mortality (HR 1.61; [95%CI: 1.46 to 1.78]) (Barone et al., 2008). Tammemagi, Nerenz, Neslund-Dudas, Feldkamp, and Nathanson (2005) reported that among BCSs, type II diabetes, hypertension and cardiovascular disease (CVD) were all associated with an increased risk of all-cause mortality with respective HRs of 1.85 (95%CI 1.47 to 2.32), 1.65 (95%CI 1.37 to 1.99) and 1.78 (95%CI 1.35 to 2.35). The risk of all-cause mortality increased with increasing BMI; however after adjusting for co-

morbidities this association disappeared, suggesting that the risks of mortality associated with overweight and obesity among BCSs were mediated through co-morbid conditions (Tammemagi et al., 2005).

2.11. Adverse effects of post-diagnosis BM gain and body composition change in BCSs

Post-diagnosis BM gain may influence survival and increase the risk of co-morbid conditions among postmenopausal BCSs (Rock & Demark-Wahnefried, 2002). Bradshaw et al. (2012) reported that, compared to BCSs who remained within 5% of their pre-diagnosis BM, those who gained >10% of their pre-diagnosis BM were 2.7 times less likely to survive (HR 2.67; [95%CI = 1.37 to 5.05]). Among never smoking BCSs, and compared to those who maintained their BMI after diagnosis, BCSs whose BMI increased by 0.5-2.0kg/m^2 and >2.0kg/m^2 had an increased relative risk (RR) of all cause mortality of 1.35 (95%CI; 1.00 to 1.82) and 1.59 (95%CI; 1.12 to 2.27) respectively (p for linear trend =0.01) (Kroenke et al., 2005). Each 5kg post-diagnosis BM gain has been associated with a 12% increase in all-cause mortality (p=0.004), a 13% increase in breast cancer mortality (p=0.01) and a 19% increase in CVD mortality (p=0.04) (Nichols et al., 2009). However, not all studies have found an association between BM gain and breast cancer recurrence, breast cancer mortality or all-cause mortality (Caan et al., 2006; Caan et al., 2008; Camoriano et al., 1990; Makari-Judson et al., 2007).

Postmenopausal BCSs may have an increased risk of bone fracture. After following a prospective cohort of postmenopausal women for nine years Chen et al. (2009) reported that the risk of hip and spinal fractures increased by 55%

and 26% respectively after breast cancer diagnosis. This is significant as, even after adjustment for key confounders, non-traumatic fractures of the hip and spine have been associated with an increased risk of mortality in women aged >50 years (Morin et al., 2011).

Post-diagnosis BM gain and body composition changes may exacerbate existing obesity related co-morbidities, increase the likelihood of new co-morbidities developing and are associated with an increased risk of adverse outcome among postmenopausal BCSs. It is clear that postmenopausal BCSs may benefit from interventions designed to prevent and/or treat the gains in BM, FM and BF% and the reductions in LBM, BMC and BMD, that may occur during the treatment and recovery stages of the breast cancer experience.

2.12. Aetiology of BM gain in BCSs

The aetiology of sarcopenic BM gain in postmenopausal BCSs has not been extensively studied. Although the underlying causes are complex, a person gains BM when the energy balance (EB) equation is unbalanced, and energy intake (EI) exceeds energy expenditure (EE) (British Nutrition Foundation, 1999).

It has been proposed that chemotherapy has a depressive effect upon metabolism (Irwin, McTiernan, Baumgartner, et al., 2005; Kroenke et al., 2005; Vance et al., 2011). However, Harvie et al. (2005), Harvie, Campbell, Baildam, and Howell (2004) and Demark-Wahnefried, Hars, et al. (1997) all reported that that resting energy expenditure (REE) did not change significantly among BCSs during the period of chemotherapy treatment. Del Rio et al. (2002) reported that when BCSs were treated with chemotherapy BM gains were accompanied

by parallel increases in REE. These findings suggest that chemotherapy does not have a depressive effect on metabolism.

Another theory is that increased EI, decreased EE, or a combination of both is responsible for the BM gains observed in postmenopausal BCSs (Irwin, McTiernan, Baumgartner, et al., 2005; Kroenke et al., 2005; Vance et al., 2011). However, although small increases in EI have been reported among postmenopausal BCSs during treatment by Harvie et al. (2005) and Del Rio et al. (2002) these increases were not significant. The findings from a larger study of 260 BCSs with a mean age of 57.5 years, indicated that compared to pre-diagnosis EI, by two years post-diagnosis EI had declined by 137kcal/d (±441; p=<0.001) (Wayne et al., 2004). A mean reduction in EI of 129.6kcal/d was reported even among BCSs who gained >3kg (Wayne et al., 2004). Although EE was not assessed in this study, 36% of BCSs had reduced their exercise levels from pre to post diagnosis (Wayne et al., 2004).

Data from a large cross sectional study indicated that habitual physical activity (PA) was the strongest predictor of BM stability among BCSs (Rock et al., 1999). Yaw et al. (2011) reported that, although no differences in EI were observed between BCSs who lost or gained BM during recovery, those who gained BM reported lower levels of PA, than those who lost BM. Similarly, Irwin, McTiernan, Baumgartner, et al. (2005) reported that lower levels of post-diagnosis recreational PA were associated with greater increases in BF% among BCSs (p for trend <0.05). However, no association was observed between change in EI and increases in BF% (Irwin, McTiernan, Baumgartner, et al., 2005). These findings suggest that reductions in PA and EE may be a stronger predictor of BM gain, than increased EI, among BCSs.

However, caution is required as all these studies used self report measures of EI, and there is a significant and widespread bias towards the underreporting of EI in free living individuals (Livingstone & Black, 2003; Livingstone et al., 1990). Underreporting of EI has been identified among BCSs enrolled on the Women's Healthy Eating and Living Study (Caan et al., 2000). Therefore, the lack of association between EI and BM gain among BCSs may be related to the underreporting of EI. Nevertheless, when accelerometers were used to objectively assess PA in BCSs, moderate-to-vigorous intensity PA was significantly negatively associated with BMI and WC (Lynch et al., 2010).

There is compelling evidence that postmenopausal BCSs reduce their PA in the post-diagnosis period. Irwin et al. (2003) reported that, compared to one year prior to diagnosis, one year after diagnosis BCSs had a statistically significant reduction in total PA of 11%, which was equivalent to two hours a week ($p=<0.05$).

Levels of PA may vary across the stages of the cancer experience, and a "V shaped" trend has been observed. Huy, Schmidt, Vrieling, Chang-Claude, and Steindorf (2012) reported that among 1067 German postmenopausal BCSs, median leisure-time PA decreased from 36.2MET·h/week prior to diagnosis to 14 MET·h/week during treatment; although one year after breast cancer surgery PA had increased to 34.0MET·h/week, it did not reach pre-diagnosis levels ($p<0.001$) (Fig.4).

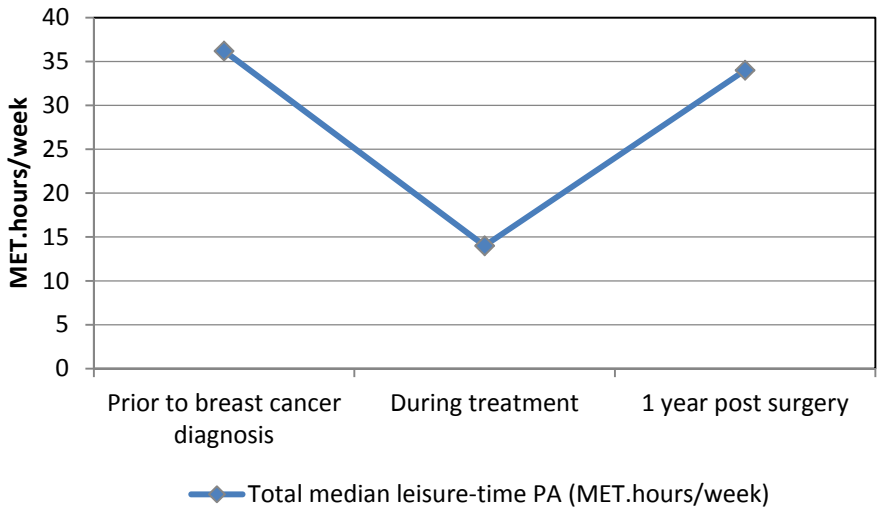

Figure 4

Levels of median leisure-time PA among German postmenopausal BCSs across the stages of the cancer experience (Adapted from Huy et al., 2012)

Littman, Tang, and Rossing (2010) observed a similar pattern among 315 BCSs; pre-diagnosis mean recreational PA was 18.8MET·h/week, one year post-diagnosis this fell to 9.2MET·h/week (p=<0.05); although PA increased to 15.02MET·h/week two and half years post-diagnosis, PA did not return to pre-diagnosis levels, and remained suppressed, by an average of 3MET·h/week over the recovery stage of the breast cancer experience.

Reductions in EE and PA appear to be the most important factor related to BM gain among postmenopausal BCSs. PA is reduced over the treatment and recovery stages of the cancer experience and does not return to pre-diagnosis levels over the longer term survivorship stage. Interventions designed to increase exercise and PA among postmenopausal BCSs may have an important role in weight management.

2.13. Exercise and PA guidelines for postmenopausal BCSs

PA has been defined as any bodily movement, produced by the contraction of skeletal muscle, which results in substantially increased EE; exercise is a subset of PA that is planned, structured and performed to improve physical fitness (Caspersen, Powell, & Christenson, 1985).

According to reports from the American College of Sports Medicine (ACSM) (Schmitz et al., 2010), the Australian Association for Exercise and Sport Science (Hayes et al., 2009), the British Association of Sport and Exercise Sciences (A. Campbell et al., 2011) and Macmillian Cancer Support (Macmillan Cancer Support, 2011) exercise is safe and beneficial for cancer survivors. It has been recommended that cancer survivors should avoid inactivity and, unless otherwise advised, should aim to follow the standard age appropriate PA guidelines for the general population (A. Campbell et al., 2011; Schmitz et al., 2010). The current UK PA guidelines for the promotion and maintenance of health in adults are outlined in Table 3 (Department of Health, 2011, pp. 32-41). Although it would seem plausible that cancer survivors who follow the general PA guidelines would acquire similar health benefits to the general population, there is little research to support this (Doyle et al., 2006; Schmitz et al., 2010). Treatments for postmenopausal breast cancer can disrupt metabolic and physiologic processes, and some postmenopausal BCSs appear to be at an increased risk of BM gain, sarcopenia and bone loss (Schmitz et al., 2010; Vance et al., 2011). Therefore postmenopausal BCSs may require higher levels of PA than the general population.

Table 3

Physical activity recommendations for the promotion and maintenance of health in adults

Recommendation	Description	Example
Physical activity recommendations for adults (19-64 years) and older adults (>65 years)		
At least 150 min (2½ hours) of moderate intensity activity in bouts of 10 minutes or more e.g. 30 minutes on at least 5 days a week.	Moderate intensity physical activities will cause adults to get warmer and breathe harder and their hearts to beat faster, but they should still be able to carry on a conversation	• Brisk walking • Cycling • Ballroom dancing
OR For those who are regularly active at moderate intensity; 75 min (1 ¼ hours) of vigorous intensity activity spread across the week	Vigorous intensity physical activities will cause adults to get warmer and breathe much harder and their hearts to beat rapidly, making it more difficult to carry on a conversation.	• Swimming • Football • Climbing stairs • Running
OR A combination of moderate and vigorous intensity activity		
AND Physical activity to improve muscle strength on at least two days a week.	Physical activities that strengthen muscles involve using body weight or working against a resistance. This should involve using all the major muscle groups	• Exercising with weights • Carrying or moving heavy loads such as groceries • Activities that involve stepping and jumping • Chair aerobics
AND Minimise the amount of time spent being sedentary for extended periods.	Reduce the amount of time spent sitting	• Reducing time spent watching TV, using the computer or playing video games • Taking regular breaks at work • Taking regular walk breaks around the garden or street • Breaking up sedentary time such as swapping a long bus or car journey for walking part of the way
Additional recommendations for older adults (>65 years)		
Older adults at risk of falls should incorporate physical activity to improve balance and co-ordination on at least two days a week	Physical activities that improve balance and coordination should improve the stability of muscles and the ability of muscles to work together smoothly	• Tai chi • Yoga
Older adults who participate in any amount of physical activity gain some health benefits, including maintenance of good physical and cognitive function. Some physical activity is better than none, and more physical activity provides greater health benefits.		

(Adapted from Department of Health, 2011, pp. 32-41)

It is vital that the characteristics of PA and exercise are reported in relation to the frequency, intensity, time and type; because manipulation of these parameters results in differing physiological and metabolic responses and differing health and fitness benefits (American College of Sports Medicine, 2006). However, historically the reporting of these characteristics in exercise intervention studies among BCSs have been poor (K. L. Campbell, Neil, & Winters-Stone, 2011). According to the ACSM Roundtable on Exercise Guidelines for Cancer Survivors there is a "need for greater specificity about the dose-response effects of specific modes of exercise training on specific end points" (Schmitz et al., 2010). And Visovsky (2006) reported that there was a lack of studies addressing the effects of exercise in older, postmenopausal, BCSs.

2.14. Exercise, BM and body composition change in BCSs: a summary of past reviews

Several reviews assessing the effect of exercise on BM and body composition among general cancer survivor populations have been published. Exercise during cancer treatment has been shown to have a small effect on BM (weighted mean effect size [WMES] -0.25, p=0.05) and BF% (WMES -0.25; p=0.04); and exercise after cancer treatment has been shown to have a small effect on BM (WMES -0.18, p=0.004), BF% (WMES –0.18; p=0.006) and BMI (WMES -0.14; p=0.002) (Speck, Courneya, Masse, Duval, & Schmitz, 2010). Fong et al. (2012) reported that PA after cancer treatment was associated with reduced BM (-1.1 kg; [95%CI; -1.6 to -0.6 kg] p<0.001) and BMI (-0.4; [95%CI; -0.6 to -0.2]; p<0.01). Winters-Stone, Schwartz, and Nail (2010) reviewed the effects of exercise on bone health in cancer survivors, but concluded that

studies were too few and too varied to draw conclusions about the effects of exercise on BMD.

A number of reviews assessing the effect of exercise on BM and body composition among specific BCSs populations have been published (Cheema, Gaul, Lane, & Fiatarone Singh, 2008; Ingram, Courneya, & Kingston, 2006; Kim, Kang, & Park, 2009; Kirshbaum, 2007; Markes, Brockow, & Resch, 2006; McNeely et al., 2006; Rooney & Wald, 2007; Stevinson, Lawlor, & Fox, 2004; White, McAuley, Estabrooks, & Courneya, 2009). Markes et al. (2006), McNeely et al. (2006) and Kim et al. (2009); all concluded that exercise resulted in small, non-significant reductions, in BM among BCSs (standardised mean difference [SMD] -1.11; [95%CI; -2.44 to 0.22]; weighted mean difference [WMD] -0.03kg; [95%CI; -0.44 to 0.38] and SMD -0.223; [95%CI; -0.495 to 0.049] respectively).

Exercise has had a greater effect on body composition than BM among BCSs (Cheema et al., 2008; Ingram et al., 2006; Kim et al., 2009; Stevinson et al., 2004; White et al., 2009). Kim et al. (2009) reported a moderate to large effect of aerobic exercise on LBM (SMD 0.721; [95%CI; 0.047 to 1.490]) and a statistically significant, moderate to large, effect on BF% (SMD -0.890; [95%CI; -1.425 to -0.355]; p=<0.001). Ingram et al. (2006) reported BF% reductions of 2.6% to 11.7% among exercising BCSs compared to increases in BF% among controls. Cheema et al. (2008) reported that progressive resistance training was associated with reduced BF% and increased LBM among BCSs, and that these adaptations were independent of BM change.

However, all these past reviews have included both premenopausal and postmenopausal BCSs. Overweight and obesity increase the risk of

postmenopausal breast cancer and reduce the risk of premenopausal breast cancer (Cancer Research UK, 2011a). Premenopausal BCSs may gain significantly more BM than postmenopausal BCSs during the treatment and recovery phases of the breast cancer experience (Vance et al., 2011). Therefore, it is possible that, exercise may have different effects on the BM and body composition of premenopausal and postmenopausal BCSs. Therefore the findings from these past reviews may not have been representative of either group, and important effects may have been disguised. Of all the reviewers, only Markes et al. (2006) included an assessment of the training stimulus provided by the included exercise interventions. No past reviews have required that all the information in relation to the frequency intensity, time and type of exercise be available. This is important as little is known about the effects of specific exercise prescriptions in BCSs (Schmitz et al., 2010).

The characteristics of exercise in relation to the frequency, intensity, time and type which will produce the optimal BM and body composition benefits in postmenopausal BCSs have yet to be established. At present there is insufficient evidence to provide specific exercise prescriptions to postmenopausal BCSs.

2.15. Aims, objectives and research questions

The aim of this systematic review was to determine if exercise interventions are effective for the prevention and treatment of BM gain, and adverse body composition change, among postmenopausal BCSs.

The objectives of this systematic review were to;

- Identify exercise intervention studies that have included measures of BM and body composition in postmenopausal BCSs.
- Describe the specific types of exercise interventions, in relation to the frequency, intensity, time, type and total duration that have included measures of BM and body composition in postmenopausal BCSs.
- Determine the effects of exercise interventions on the BM, BMI, WC, LBM, FM, BF%, WC, BMC and BMD of postmenopausal BCSs.

The specific research questions this systematic review sought to answer were;

1. **Do exercise interventions have a beneficial effect on the BM and body composition (↓BM, ↓BMI, ↓WC, ↑LBM, ↓FM, ↓BF%, ↑BMC and ↑BMD) of postmenopausal BCSs?**

2. **Which specific types of exercise, in relation to frequency, intensity, time, type and total duration, have been used to potentially prevent or treat BM gain and adverse body composition change (↑BM, ↑BMI, ↑WC, ↓LBM, ↑FM, ↑BF%, ↓BMC and ↓BMD) in postmenopausal BCSs?**

As recommended by the Centre for Research and Dissemination (2009, pp. 7-9) and the Cochrane Collaboration (O'Connor, Green, & Higgins, 2011) the research questions were clearly defined and framed using the Population(s), Intervention(s), Comparator(s), Outcome(s) and Study Design (PICOS)

structure. Descriptions of each of the PICOS elements, as they relate to this systematic review, are outlined in Table 4. Refer to the glossary, attached in Appendix 1, for detailed definitions of terms.

Table 4

Description of the PICOS elements included in the systematic review of the effects of exercise on BM and body composition in postmenopausal BCSs

PICOS	Description
Population	• Studies of participants, who were female and were classified as postmenopausal BCSs. • Studies of participants with mixed cancer diagnoses if outcomes were reported separately for postmenopausal BCSs. • Studies of participants with mixed menopausal statuses if outcomes were reported separately for postmenopausal BCSs.
Interventions	• Any exercise only intervention, of aerobic or resistance exercise, or a combination of aerobic and resistance exercise, that took place during or after treatment for postmenopausal breast cancer, and for which the frequency, intensity, time, type and total duration were reported. • Any multi-faceted intervention (e.g. exercise and diet, exercise and cognitive behavioural therapy [CBT], exercise and nutritional supplements) where the exercise intervention met the above criteria and where data for an exercise only group was available.
Comparators	• Postmenopausal BCSs assigned to usual care. • Non-exercising postmenopausal BCS. • Postmenopausal BCSs asked to continue with usual level of exercise and PA. • Postmenopausal BCSs assigned to placebo exercise interventions with minimal effects on EE e.g. stretching.
Outcomes	• Any specified body composition outcome. Specified body composition outcomes were WC, LBM, FM, BF%, BMD and BMC. • Any specified BM outcome, when reported in combination with any specified body composition outcome. Specified BM outcomes were BM and BMI.
Study designs	• Randomised Controlled Trials (RCTs) including parallel group trials, randomised cross-over trials and cluster randomised controlled trials

3.0. Methodology

3.1. Overview of the systematic review process

In order to be valid a systematic review must be based on the best available evidence. Systematic reviews should; use a clearly stated reproducible methodology that attempts to minimise bias, use a systematic search strategy that attempts to identify all studies that meet pre-defined eligibility criteria, make an assessment of the methodological quality of individual studies and synthesise and present findings in a systematic way (Centre for Reviews and Dissemination, 2009, p. 9; Green et al., 2011).

This systematic review was developed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). A completed PRISMA 21 item checklist of systematic review reporting items is provided in Appendix 6.

This systematic review was conducted in fulfilment of an MSc dissertation and therefore all review processes were conducted by a single reviewer.

3.2. Minimising the risk of bias at the review level

Bias occurs when obtained results are systematically different to the true effects therefore, the conclusions drawn from biased results may be misleading or wrong (Centre for Reviews and Dissemination, 2009, p. 262; Crombie, 1996, p. 18). There are a number of types of reporting bias that can affect the validity of a systematic review. For definitions and examples of reporting bias refer to Table 5.

Table 5

Definitions and evidence of different types of reporting bias

Type of Bias	Definition	Evidence
Publication bias	The publication or non-publication of research findings, depending on the nature and direction of the results	• Studies with significant results are more likely to be published than those with null or negative findings. • Studies with positive results were more likely to be published as scientific papers than studies with inconclusive results (adjusted odds ratio 4.59; 95%CI; 2.21 to 9.54) (Decullier, Lheritier, & Chapuis, 2005). • Clinical research studies with statistically significant results were more likely to be published than those with null results (odds ratio 2.32; 95%CI 1.25 to 4.28) (Easterbrook, Berlin, Gopalan, & Matthews, 1991). • Clinical trials with positive results were nearly four times more likely to be published than those with negative results (odds ratio 3.90; 95%CI; 2.68 to 5.68) (Hopewell, Loudon, Clarke, Oxman, & Dickersin, 2009). • Cohort studies with positive results were 2.78 times more likely to be published than those with negative results (odds ratio 2.78; 95%CI; 2.10 to 3.69) (Song et al., 2009). • Clinical research trials with positive results (p=<0.05) were more likely to be published than those with null or negative results (HR 2.32; 95%CI; 1.47 to 3.66 [p=0.0003]) (Stern & Simes, 1997).
Time lag bias	The rapid or delayed publication of research findings, depending on the nature and direction of the results	• Studies with significant results have a shorter time to publication. • Studies with positive results were published more quickly than studies with inconclusive results (HR 2.48; 95%CI; 1.36 to 4.55) (Decullier et al., 2005). • Clinical trials with statistically significant positive results were published one to three years earlier than those with negative or null results (4-5yrs vs 6-8yrs) (Hopewell, Clarke, Stewart, & Tierney, 2007). • Randomised efficacy trials with positive results (p=<0.05) had a significantly shorter time to publication than those with null or negative results (4.3yrs vs 6.5yrs; HR 3.7; 95%CI; 1.8 to 7.7 [p=0.001]) (Ioannidis, 1998). • Clinical research trials with positive results (p=<0.05) had a significantly shorter time to publication than those with null or negative results (4.7yrs vs 8.0yrs; HR 3.13; 95% CI 1.76 to 5.58 [p=0.0001]) (Stern & Simes, 1997).
Duplicate publication bias	The multiple or singular publication of research findings, depending on the nature and direction of the results	• Studies with significant results are more likely to be published repeatedly. • Studies with significant results were more likely to lead to a greater number of publications (Easterbrook et al., 1991). • Out of 244 research trials investigating non-steroidal anti-inflammatory drugs in rheumatoid arthritis. 44 (18%) were multiple publications; 20 trials were published twice, ten trials three times, and one trial four times (Gotzsche, 1989).

Table 5; Definitions and evidence of different types of reporting bias /cont.

Type of Bias	Definition	Evidence
Location bias	The publication of research findings in journals with different ease of access or levels of indexing, depending on the nature and direction of results	• Studies not indexed in MEDLINE, and those found in the grey literature, are more likely to show a greater treatment effect Studies with significant results are more likely to be located in low impact factor journals. • Compared to trials published in MEDLINE-indexed journals treatment effect estimates were on average 6% more beneficial for trials not indexed in MEDLINE (95%CI; 18% more beneficial to 7% less beneficial; p= 0.35) (Egger, Juni, Bartlett, Holenstein, & Sterne, 2003). • On average published trials showed a 9% greater all over treatment effect than trials located in the grey literature (OR for grey versus published trials 1.09; 95%CI; 1.03 to 1.16) (Hopewell, McDonald, Clarke, & Egger, 2007). • Journals with low or no-impact factor are more likely to report studies with significant results than journals with a high impact factor (p=<0.05) (Pittler, Abbot, Harkness, & Ernst, 2000).
Citation bias	The citation or non-citation of research findings, depending on the nature and direction of the results	• Studies with significant results are more likely to be cited. • Trials with positive results were 2.8 times more likely to be summarised (cited) in the secondary literature than trials catalogued in MEDLINE (OR 2.8; 95%Ci; 2.02 to 3.93; p<0.001) (Carter, Griffin, & Carter, 2006). • Out of 111 research trials investigating non-steroidal anti-inflammatory drugs in rheumatoid arthritis, 44 (49%) had a significant positive citation bias (Gotzsche, 1987). • In trials of cholesterol lowering in CHD, studies which had a positive effect were cited almost six times more often than those which demonstrated a null or negative effect (mean annual citations 40 vs. 7.4) (Ravnskov, 1992).
Language bias	The publication of research findings in a particular language, depending on the nature and direction of the results	• Studies with significant results are more likely to be published in English. • RCT in the German language were more likely to be published in an English-language journal if the results were statistically significant (odds ratio 3·75; 95%CI 1·25 to 11·3) (Egger et al., 1997). • Compared to English language trials treatment effect estimates were on average 16% more beneficial in non-English language trials (95% CI; 3% to 26%;[*p* = 0.011]) (Egger et al., 2003). • Compared to English language clinical trials, non English language trials were more likely to produce significant results at the p=<0.05 level (41.7% vs 31.3%; p=0.033) (Juni, Holenstein, Sterne, Bartlett, & Egger, 2002).
Outcome reporting bias	The selective reporting of some outcomes but not others, depending on the nature and direction of the results	• Studies with significant results are more likely to fully report all outcomes. • Within a trial, incompletely reported outcomes had a higher odds of being statistically non-significant compared with fully reported outcomes (OR 2.0; 95%CI; 1.6 to 2.7) (Chan & Altman, 2005). • When compared to trial protocols, 62% of published articles had at least one primary outcome that was changed on publication. Statistically significant outcomes had a higher odds of being fully reported compared with non-significant outcomes (OR; 2.4; 95%CI; 1.4 to 4.0) (Chan, Hrobjartsson, Haahr, Gotzsche, & Altman, 2004). • RCT with statistically significant outcomes had a higher odds of being fully reported compared to those with non-significant outcomes (range of odds ratios: 2.2 to 4.7) (Dwan et al., 2008).

Studies with statistically significant results are more likely to be published than those with null or negative findings, leading to publication bias (Centre for Reviews and Dissemination, 2009; Egger & Smith, 1998; Sterne, Egger, & Moher, 2011). Other forms of reporting bias include; publication bias, time-lag bias, duplicate publication bias, location bias, citation bias, language bias and outcome reporting bias (Table 5) (Centre for Reviews and Dissemination, 2009, pp. 12-13; Sterne et al., 2011). To minimise the effects of reporting bias systematic reviews must adopt a comprehensive search strategy. This search strategy must have been designed to identify and include all relevant studies, regardless of publication status, otherwise the findings may be biased towards the positive and overestimate the effect of an intervention (Centre for Reviews and Dissemination, 2009, pp. 12-13; Egger & Smith, 1998; Hopewell et al., 2009; Sterne et al., 2011).

3.3. Search strategy

A search strategy should aim to achieve a high sensitivity, so as to detect all relevant articles, however such a strategy may result in low specificity, where large numbers of unrelated articles are detected (Lefebvre, Manheimer, & Glanville, 2011). In this instance, as only a single reviewer was available, it was necessary to carefully balance sensitivity and specificity to take account of the human and material resources available.

3.4. Search terms

The Cochrane Collaboration recommends limiting the number of concepts used in systematic review searches (Lefebvre et al., 2011). Initial scoping literature review revealed that menopausal status and body composition outcomes were

often not reported in the title or abstract of studies of exercise interventions among BCSs. Therefore initial basic search terms were limited to the population and the interventions of interest. The search terms; cancer, breast and exercise were applied in isolation to two general (MEDLINE and Cumulative Index to Nursing and Allied Health Literature [CINAHL]) and one specific (Sports Discus) electronic bibliographical database (all searches were conducted on 25th May 2012). These initial searches were performed in order to gauge if this strategy would return a manageable number of records. The limit for a manageable number of records was set at 2000 (arbitrary figure). It became clear that this strategy would return an unmanageable number of records (Table 6). Therefore the basic search terms were combined with the Boolean operator "AND" to limit the search and make it more specific. It was determined that this strategy would return a manageable number of records (Table 6) and this strategy formed the structure for the extensive search.

Table 6

Number of records returned from the initial basic search strategy

Search Terms	Number of records retrieved from MEDLINE	Number of records retrieved from CINHAL	Number of records retrieved from Sports Discus
Cancer	2628869	137694	14885
Breast	308119	60279	4467
Exercise	237634	76606	171572
Breast AND Cancer AND Exercise	1632	863	469

The Cochrane Collaboration advocate the use of extensive keywords and phrases to expand the search in each concept area by the use of the Boolean

operator “OR” (Lefebvre et al., 2011). Therefore two lists of keywords and phrases, which related to the populations and interventions of interest, were generated from studying relevant reviews and Medical Subject Headings (MESH) (Table 7).

Table 7

Key words and phrases related to BCSs populations and exercise interventions

Key words and phrases related to the population: **Breast cancer survivors**	Key words and phrases related to the intervention: **Exercise**
Breast Cancer	Exercise
Breast Neoplasm	Exercise Intervention
Breast Carcinoma	Exercise Program
Breast Tumor	Exercise Programme
Breast Tumour	Exercise Training
Mammary Cancer	Exercise Therapy
Mammary Neoplasm	Rehabilitation
Mammary Carcinoma	Physical Activity
Mammary Tumor	Physical Activity Intervention
Mammary Tumour	Physical Therapy
Ductal Carcinoma in Situ	Physical Fitness
Lobular Carcinoma in Situ	Aerobic Exercise
Invasive Ductal Breast Cancer	Aerobic Training
Ductal Carcinoma	Aerobics
Invasive Lobular Breast Cancer	Resistance Exercise
Lobular Carcinoma	Resistance Training
Invasive Breast Cancer	Weight Training
Breast Cancer Patient	Weight Lifting
Breast Cancer Survivors	Muscle Strengthening
Breast Cancer Survivorship	Walking
Breast Cancer Recovery	Running
Breast Cancer Treatment	Jogging
	Cycling
	Rowing
	Racing

The keywords and phrases presented in Table 7 were applied to the extensive search strategy.

3.5. Electronic bibliographical database searches

A comprehensive database search is required to minimise bias (Lefebvre et al., 2011). As the topic of exercise and cancer survivorship spans a wide range of research disciplines it was necessary to search a wide range of specialist databases to locate relevant literature (Stevinson & Lawlor, 2004). Details of the electronic bibliographical databases that were searched are provided in Table 8. These databases were either freely available or were available via University of Chester subscriptions.

Initial literature searches revealed that the earliest published study investigating the effects of exercise on body composition in BCSs was performed in 1989 (Winningham, MacVicar, Bondoc, Anderson, & Minton, 1989). Therefore bibliographical databases were searched for studies from 1989 onwards. Initially searches were performed up to the end of April 2012 and this was updated once, up to the end of June 2012.

To improve the precision of the searches, and reduce the number of unrelated studies returned, wherever possible searches were limited by species (humans), gender (female), and age (adults 19+ years).

Full details of the electronic bibliographical search strategy used, and the number of records returned, are provided in Appendices 7 and 8.

Table 8

Descriptions of the bibliographical databases searched

Database	Summary of coverage	Access Method	Dates Searched
PubMed - MEDLINE	**Covers biomedical literature** Provides citations (sometimes with full text links) to >21 million citations from MEDLINE, life science journals, and online books.	PubMed interface	1989 - End June 2012
The Cochrane Library	**Covers evidence to inform healthcare decision-making** A collection of six databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register, Health Technology Assessment Database NHS Economic Evaluation Database) that contain different types of high-quality, independent research	Freely Available	1989 - End June 2012
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	**Covers health and social care** Includes coverage of >3000 health-related journals and provides full text for >560 journals. Also includes selected pamphlets, dissertations and foreign language studies with English abstracts.	EBSCO interface	1989 - End June 2012
ProQuest Nursing & Allied Health Source	**Covers nursing, allied health, alternative and complementary medicine** Provides abstracts for >850 titles, >715 full text titles and >12,000 full text dissertations.	PROQUEST interface	1989 - End June 2012
Sports Discus	**Covers all sports science disciplines** Provides references (sometimes with abstracts) to articles from >2,000 journals.	EBSCO interface	1989 - End June 2012
Physiotherapy Evidence Database (PEDro)	**Covers physiotherapy disciplines** A database of >21,000 RCT, systematic reviews and clinical practice guidelines.	Freely Available	1989 - End June 2012

3.6. Grey literature searches

Research reports, policy documents, book chapters, conference abstracts, dissertations, personal correspondences and unpublished data are all examples of grey literature (Hopewell, McDonald, et al., 2007). The inclusion of grey literature in a systematic review may help to overcome some of the problems of publication bias. Two sources of grey literature are the ZETOC database and the SCIRUS search engine. ZETOC is an electronic database of abstract only listings of >20,000 current journals and >16,000 conference proceedings held at the British Library. SCIRUS is a science-specific search engine which searches >460 million science-specific Web pages. The ZETOC database and the SCIRUS search engine were searched to locate sources of grey literature; full details these searches are provided in Appendices 9 and 10 respectively.

A number of relevant book chapters, from the following books, were hand searched in order to locate relevant records.

- Courneya, K. S., & Friedenreich, C. M. (Eds.). (2011). *Physical Activity and Cancer: Recent Results in Cancer Research* (Vol. 186). Heidelberg: Springer.

- Irwin, M. L. (Ed.). (2012). *ACSM's Guide to Exercise and Cancer Survivorship*. Champaign; IL: Human Kinetics

- McTiernan, A. (Ed.). (2006). Cancer Prevention and Management through Exercise and Weight Control. Boca Raton; FL: CRC Press.

- Saxton, J., & Daley, A. (Eds.). (2010). Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life. New York: Springer.

Full details of the book chapters searched are provided in Appendix 11.

3.7. Sources Handsearched

Handsearching requires a journal to be checked from cover to cover; each item (full reports, short reports, editorials, correspondence sections, meeting abstracts, supplements and letters) should be read to determine relevance to the review (Hopewell, Clarke, Lefebvre, & Scherer, 2007). Handsearching can locate records not retrieved by the search terms, or those not indexed in electronic bibliographical databases; therefore handsearching can help to minimise publication bias (Centre for Reviews and Dissemination, 2009, p. 18; Hopewell, Clarke, Lefebvre, et al., 2007).

The online versions of the following journals were handsearched;

- **British Journal of Sports Medicine**
- **Journal of Cancer Survivorship**
- **Cancer, Epidemiology, Biomarkers and Prevention**
- **Medicine & Science in Sport and Exercise**
- **Oncology Nursing Forum**
- **Psycho-Oncology**
- **International Journal of Sports Medicine**
- **Journal of Clinical Oncology**

The online versions of these journals were accessed from freely accessible sources or via subscriptions held by the University of Chester. All supplements, letters and conference proceedings were searched; however, online full-text access, to the International Journal of Sports Medicine and the Journal of Clinical Oncology were not available, therefore handsearches of titles and

abstracts were made. Journals were searched from inception or from January 1989, whichever was earlier. Initial searches were conducted up to the end of April 2012 and were updated up to the end of June 2012. Full details of the specific journal handsearches are provided in Appendix 12.

3.8. Data management

Endnote citation management software (Adept Scientific, 2011) was used to document the search process and streamline document management (Centre for Reviews and Dissemination, 2009; Lefebvre et al., 2011, p. 21). All records located by the search strategy were exported, or entered manually, into Endnote (Adept Scientific, 2011) where records were merged and duplicate records were removed.

3.9. Screening records to determine inclusion or exclusion into the systematic review

In order to remove obviously irrelevant reports as efficiently as possible, the titles and abstracts of all records were screened against basic initial eligibility criteria (Table 9). A single failed eligibility criterion is sufficient for a study to be excluded from a review (Higgins & Deeks, 2011). Therefore eligibility criteria were applied in order of importance and the first 'no' response was used as the primary reason for exclusion. The initial eligibility screening criteria were applied cautiously and were generally over-inclusive, so as to avoid inadvertently excluding a potentially relevant record.

Table 9

Initial eligibility screening criteria

PICOS concept area	Inclusion / exclusion criteria
Study Design	• Was the study primary research? • Was the study a RCT?
Population	• Did the study include human subjects? • Did the study include adult (>18 years) subjects? • Did the study include female subjects? • Did the study include subjects who were BCS?
Intervention	• Was the intervention aerobic or resistance exercise, or a combination of aerobic and resistance exercise? • Was the exercise intervention applied after the diagnosis of breast cancer?

In an attempt to quantify the extent of English language bias the existence of non-English language records were documented (Centre for Reviews and Dissemination, 2009). Non-English language records, for which an English language title and abstract were available, were screened and excluded in accordance with the initial eligibility criteria.

The full-text versions of any records remaining after initial eligibility screening were obtained from; freely available sources, subscriptions held by the University of Chester and, when not available from these two sources, from the British Library via the University of Chester's inter-library loan service.

Full-text articles were screened against the full eligibility criteria outlined in Table 10. Refer to the glossary, attached in Appendix 1, for full definitions of inclusion or exclusion criteria terms.

Table 10

Full eligibility screening criteria

PICOS	Inclusion criteria	Exclusion criteria
Study Design	• Was the study published in English language? • Was the study published fully? • Was the study primary research? • Was the study a RCT?	• Published in languages other than English. • Abstract only publications • Review articles, RCT study designs/protocols, proposed studies, editorials, news items and letters. • Study designs other than RCTs.
Outcome	• Did the study include one or more of the specified body composition outcomes (WC, LBM, FM, BF%, BMC and BMD)? • Did the study include one or more specified BM outcome (BM, BMI) when in combination with one or more specified body composition outcome? • Did the study include body composition and BM outcomes available for pre and post exercise intervention?	• No specified body composition outcome (WC, LBM, FM, BF%, BMC and BMD) • BM (BM, BMI) only outcomes. • Specified outcome data not available pre and post intervention.
Population	• Did the study include human subjects? • Did the study include adult subjects (>18yrs)? • Did the study include female subjects? • Did the study include postmenopausal subjects? • OR if menopausal status was not reported; • Did the study only include subjects >50 years? • Did the study include BCSs?	• Non BCSs populations. • Mixed cancer survivor populations (unless data for a specific breast cancer group could be isolated). • Mixed premenopausal and postmenopausal BCSs populations (unless data for a specific postmenopausal BCSs group could be isolated). • If menopausal status was not reported; populations containing subjects <50yr, (unless data for a specific >50yrs group could be isolated).
Comparators	• Were the controls postmenopausal BCSs? AND • Were controls assigned to usual care? OR Asked to continue with usual level of exercise and PA? OR Asked not to exercise? OR Assigned to a placebo exercise intervention with a minimal effect on EE e.g. stretching?	• Non postmenopausal BCS controls • Postmenopausal BCS controls who were assigned to an exercise placebo with a >moderate effect on EE.

Table 10; Full eligibility screening criteria /cont.

PICOS	Inclusion criteria	Exclusion criteria
Intervention	• Was the intervention aerobic exercise or resistance exercise or a combination of aerobic and resistance exercise? • Did the exercise take place after diagnoses of breast cancer (either during or after completion of primary treatment)? • Was a full description of the exercise in relation to the; frequency, intensity, time and type reported? • Did the exercise intervention meet the criteria for a high quality training study? • (see Appendix 11 for details)	• Exercise interventions with a nominal effect on EE (e.g. movement therapy, stretching, yoga) • Exercise inventions which were part of a multi-component intervention e.g. exercise-diet or exercise-CBT (unless data relating to an exercise only group was available)

Due to feasibility issues relating to translation, non-English language reports were excluded at this stage (Centre for Reviews and Dissemination, 2009). Initial literature review revealed that abstract only publications would be unlikely to provide the level of detail required to determine inclusion or exclusion. Therefore abstract only publications were excluded at this stage. In order to allow the effects of exercise to be isolated, studies which included exercise as part of a complex multi-component intervention (e.g. exercise/diet; exercise/nutritional supplement, exercise/CBT, exercise/counselling) were excluded. Many studies of BCSs do not report menopausal status, therefore it was decided that studies which included subjects under the age of 50 years, the average age of the menopause, would be excluded.

Exercise interventions should provide an adequate training stimulus that would be likely to result in BM and body composition adaptations; an inadequate training stimulus may lead to non-significant findings. Therefore an Assessment of High Quality Training Studies (HQTS) tool was used to determine if the

exercise intervention studies considered for inclusion in this review provided an adequate training stimulus (Markes et al., 2006). Full details of the HQTS tool and the HQTS assessment of studies meeting all other eligibility criteria are provided in Appendix 13.

All studies that met the full eligibility criteria were included in the final review.

3.10. Dealing with duplicate publications

In an attempt to identify duplicate publications; the names of the authors, the locations and settings, the specific details of the interventions, the numbers of participants, the baseline characteristics of the participants and the dates and durations of all studies that met the full eligibility criteria were compared (Higgins & Deeks, 2011). Any duplicate publications that were identified were treated as a single study, but references were made to all publications in the final review (Centre for Reviews and Dissemination, 2009, p. 25).

3.11. Assessing the risk of bias of individual studies

The terms methodological quality and risk of bias are often used interchangeably (Hartling et al., 2009; Higgins, Altman, & Sterne, 2011). For the purposes of this review, risk of bias refers to the internal validity of the study (the way in which the study has been designed and conducted), whereas methodological quality refers to all other aspects of quality (including the adequacy of reporting).

In order to ensure this systematic review was valid, and based on the best quality evidence, only RCTs were considered for inclusion. However, although RCTs are associated with a lower risk of bias than other study designs, not all

studies of the same design are equally well designed and conducted (Centre for Reviews and Dissemination, 2009; Higgins et al., 2011). There is evidence that inadequate sequence generation (Schulz, Chalmers, Hayes, & Altman, 1995), inadequate allocation concealment (Egger et al., 2003; Schulz et al., 1995), lack of double blinding (Schulz et al., 1995) and the selective reporting of outcomes (Chan & Altman, 2005; Chan et al., 2004) are associated with overestimates of treatment effects (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2010; Centre for Reviews and Dissemination, 2009, p. 33; Hartling et al., 2009; Higgins et al., 2011). Therefore, in order to determine if the findings from individual studies were valid, assessments of the risk of bias were made for each of the studies that were included in this systematic review.

There are many methods used to assess the methodological quality of studies, these include scales and checklists (Higgins et al., 2011). Moher et al. (1995) indentified 25 scales and 9 checklists and Armijo-Olivo et al. (2008) indentified 21 scales that could be used to assess the quality of RCTs. However despite the large number of quality assessment tools, only a minority have been rigorously developed and tested for validity and reliability (Armijo-Olivo et al., 2008; Deeks et al., 2003; Moher et al., 1995; Moher, Jadad, & Tugwell, 1996).

There is no validated methodological quality assessment tool specifically designed for exercise intervention studies (Armijo-Olivo et al., 2008; Stevinson et al., 2004). True double blinding in exercise intervention studies is often impractical or impossible, as participants will know whether or not they are performing exercise (Armijo-Olivo et al., 2008; Han et al., 2004; Yeh, 2008; Yeh, Wang, Wayne, & Phillips, 2009). Therefore, many methods that are commonly used to assess methodological quality may not be appropriate for

exercise intervention studies, due to the focus many of them place on participant blinding.

Past systematic reviews of exercise and body composition in BCSs have used a variety of quality assessment tools; Kim et al. (2009) used the Jadad scale (Jadad et al., 1996), Cheema et al. (2008) used the Delphi List (Verhagen et al., 1998), Ingram et al. (2006) used the Effective Public Health Practice Project tool (Effective Public Health Practice Project, 2003), Markes et al. (2006) used the van Tulder criteria (van Tulder, Assendelft, Koes, & Bouter, 1997) and Kirshbaum (2007) and McNeely et al. (2006) developed their own quality assessment tools. It is therefore possible to conclude that there is no consensus of opinion as to which is the most suitable quality assessment tool to use when reviewing exercise and breast cancer survivorship research.

Higgins et al. (2011) stated that there was a lack of clarity as to what many of the scales and checklists currently used to assess methodological quality were actually measuring, as many include items relating to the quality of reporting, as well as items relating to the risk of bias. In recent years there has been a considerable effort to improve the reporting of RCTs; this has primarily been driven by the Consolidated Standards of Reporting Trials (CONSORT) Statement (Begg et al., 1996; Moher et al., 2010; Schulz, Altman, Moher, & Group, 2010). The CONSORT statement includes a 25 item checklist (Appendix 14). A RCT that does not adhere to the CONSORT statement is not completely and transparently reported; as a consequence it may be difficult for reviewers to assess the conduct, reliability or validity of the trial (Hopewell, Dutton, Yu, Chan, & Altman, 2010; Moher et al., 2010; Schulz et al., 2010).

Although the quality of reporting of RCTs has improved in recent years, in 2006 a significant number of RCTs were still not reporting fully, and the quality of reporting remained well below an acceptable level (Hopewell et al., 2010; Moher et al., 2010; Plint et al., 2006). This is of particular importance as RCTs of exercise interventions are more complex than many pharmacological RCTs, and therefore may require more detailed reporting (Armijo-Olivo et al., 2008). As the field of exercise and cancer survivorship is still emerging, it was decided that assessments of both the risk of bias, and the quality of reporting, would be beneficial and may improve the quality of future research.

Brouwers et al. (2005) and Juni, Witschi, Bloch, and Egger (1999) reported that there was considerable variation in the classification of studies as high or low quality as a function of the scale or checklist that was applied. Therefore caution should be applied if quality rating scales are used to restrict the number of studies included in a systematic review; as the choice of scale will determine which studies are eligible (Brouwers et al., 2005; Juni, Altman, & Egger, 2001). As studies considered for inclusion into this systematic review were limited to RCTs, it was decided not to exclude studies on the basis of methodological quality assessment classification; but rather use the assessment of methodological quality to determine the quality of research that has been conducted and to identify areas of improvement for future research.

In response to the lack of validity, variations in the classification of quality and the lack of clarity as to what is being measured by many methodological quality assessment tools, the Cochrane Collaboration no longer advocate the use of quality scales and checklists to assess methodological quality (Higgins et al., 2011). Instead the Cochrane Collaboration Risk of Bias Tool is recommended

(CCRBT) (Higgins et al., 2011). The CCRBT tool is based on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias (Higgins et al., 2011). However Armijo-Olivo et al. (2010) and Hartling et al. (2009) reported that certain aspects of the CCRBT were associated with low inter-rater reliability, and concluded that this was due to the subjective nature of some of the CCRBT domains. The CCRBT requires thorough training to be used effectively and requires users to have experience of making risk of bias assessments (Hartling et al., 2009). Therefore the CCRBT was not considered appropriate for use in this review, as the single reviewer was inexperienced.

Of all the methods available, the Downs and Black Checklist (1998) was considered the most appropriate tool to use to assess the methodological quality of studies included in this systematic review (Appendix 15). This checklist was developed by public health specialists, to assess the methodological quality of randomised and non-randomised health care interventions. It has been assessed for reliability and validity and scored highly for internal consistency (Kuder-Richardson 20 [KR-20] = 0.89), test-retest reliability (r = 0.88) and inter-rater reliability (r = 0.75) (Downs & Black, 1998). There is clarity of the concepts measured, as five subscales are used; reporting, external validity, internal validity-bias, internal validity -selection bias and power.

It has been suggested that methodological quality checklists might need to be adapted based on the nature of the review and the type of studies to be included (Centre for Reviews and Dissemination, 2009; Deeks et al., 2003). Given that it is virtually impossible for exercise intervention studies to blind

participants to the intervention they receive, consideration was given to the removal of question 14 (that related to participant blinding) from the Downs and Black Checklist (1998). However, lack of double blinding has been associated with a 17% exaggeration of the treatment effect, and whilst exercise intervention studies may be of the highest methodological quality, the risk of bias that results from the participants knowledge of their intervention status still exists (Higgins et al., 2011; Schulz et al., 1995). Therefore, so as to ensure the risk of bias was properly assessed, it was decided to leave question 14 in the checklist. Using the Downs and Black Checklist (1998) in an unmodified form also allowed validity to be maintained.

3.12. Methodological quality assessment using the Downs and Black Checklist (1998)

All studies that the met the full eligibility criteria were included in the final review and were rated for methodological quality using the Downs and Black Checklist (1998) (Appendices 15 and 16). The Downs and Black Checklist (1998) had 27 questions spread across five subscales; the reporting subscale (10 questions), the external validity subscale (3 questions), the internal validity (bias) subscale (7 questions), the internal validity (selection bias) subscale (6 questions) and the power subscale (1 question). Each question was scored either 0 or 1, apart from question 2 in the reporting subscale, which was scored from 0 to 2, and question 27 in the power subscale, which was scored from 0 to 5. This gave an overall score of 32, and subscale scores of 11, 3, 7, 6 and 5 for the reporting, external validity, internal validity (bias), internal validity (selection bias) and power subscales respectively (Appendix 15). In order to summarise and

compare the methodological quality of studies included in the review, overall and subscale percentage scores were calculated for each study. The higher the score, both overall and for each subscale the higher the methodological quality.

3.13. Data extraction

Extraction of data from studies can be a subjective process, therefore to minimise bias, a standardised data extraction tool was used (Centre for Reviews and Dissemination, 2009, pp. 28-32; Higgins & Deeks, 2011). A data extraction tool should obtain data that relates specifically to the objectives of the review (Centre for Reviews and Dissemination, 2009, pp. 28-32; Higgins & Deeks, 2011). To this end, a data extraction tool was developed that focused on the specific elements of the PICOS that were relevant to the review questions. Different studies were likely to present their findings in slightly different ways (e.g. mean change or % change) therefore the mean change (from pre to post intervention) for the control and exercise groups were recorded (or calculated if not available). The difference in mean change between exercisers and controls was calculated for each outcome (BM, BMI, WC, LBM, FM, BF%, BMC and BMD). This was done to standardise data collection across studies and enable comparisons of the effect of different exercise prescriptions on body composition and BM between studies to be made. Any statistically significant findings reported by individual studies were highlighted in red. It was not possible to provide standard deviations or 95% CIs, as this level of data was not reported by all studies.

To ensure that he data extraction form functioned well and was efficient i.e. did not collect irrelevant information but collected all required information, it was piloted on a number of studies generated from the initial search (Centre for Reviews and Dissemination, 2009, pp. 28-32; Higgins & Deeks, 2011).

The data extraction tool was applied to all studies that met the full inclusion criteria. A blank copy and an example of a completed data extraction form are attached in Appendices 17 and 18.

Where a study had two or more groups or subsets of exercising postmenopausal BCSs, data extraction was performed, and results were presented, for each group or subset.

4.0. Results

4.1. Identification of records and study selection

The flow of records through the systematic review, from detection to final inclusion, is presented in Figure 5.

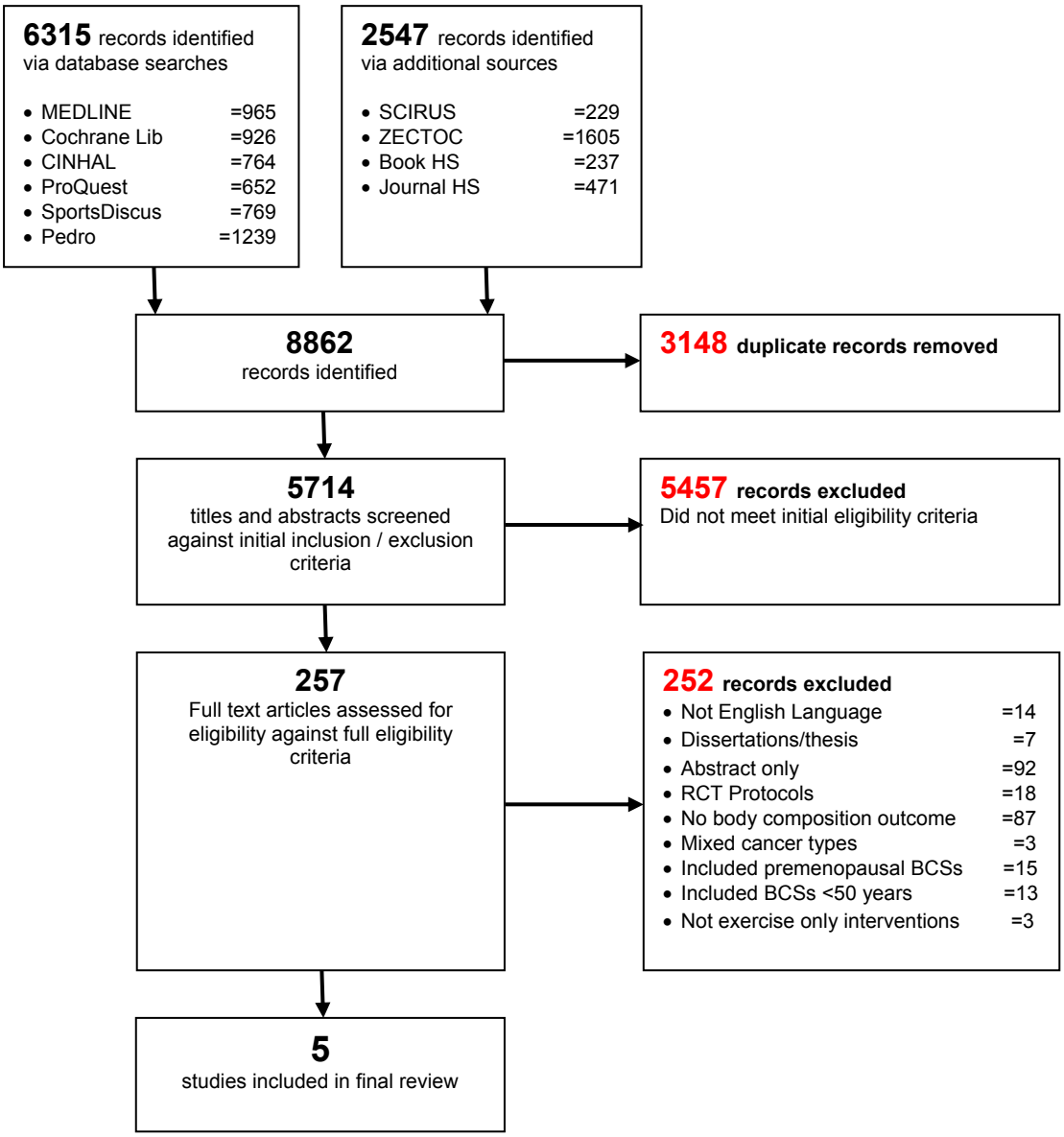

Figure 5

Flow of information through the different phases of the systematic review

The search strategy identified a total of 8862 records; after duplicate records were removed 5714 records remained (Fig. 5). Following application of the initial eligibility criteria 5474 records were excluded, and 257 full text articles were screened against the full eligibility criteria; 252 were excluded (see Fig. 5 for reasons). Five studies met the full eligibility criteria and were included in the final review (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009; Rahnama, Nouri, Rahmaninia, Damirchi, & Emami, 2010; Saarto et al., 2012; Winters-Stone et al., 2011). The search locations and retrieval methods for all of the studies included in the final review are given in Appendix 19.

One included study had two subsets of postmenopausal BCSs; one subset exercised for 6 months and the other subset exercised for 12 months (Irwin, Alvarez-Reeves, et al., 2009 [6 month and 12 month]). The results for each of these subsets are reported separately; effectively meaning results are presented for six studies. The study of Saarto et al. (2012) included a premenopausal and a postmenopausal subset of exercising BCSs; only the results from the postmenopausal subset are presented.

4.2. Study characteristics

Studies took place in Finland, Iran, Spain and USA and were published between 2006 and 2012 (Table 11). Across all studies a total of 278 postmenopausal BCSs were randomised to exercise interventions and 274 were randomised to control conditions. However 25 exercisers and 25 controls appear in the analysis twice, as these BCSs formed the 12 month exercise subset in the Irwin, Alvarez-Reeves, et al. (2009) study.

Table 11

Characteristics of studies and participants

	Study	Study Location	Sample Size (n)	Attrition Rate (%)	Mean Age (Years)	Mean BM (kg)	Mean BMI (kg/m2)	Breast cancer stage	Type of treatment	Hormone Treatment
Controls	Herrero et al. (2006)	Spain	10	20	51 ± 10	67.7 ± 8.9	24 ± 3.2	I-II	SUR + CT + RT	na
Exercisers			**10**	**20**	**50 ± 5**	**66.7 ± 10.5**	**25.1 ± 3.5**			
Controls	Irwin et al. (2009) 6 month	USA	38	15.8	55.1 ± 7.7	78.4 ± 20.0	29.7 ± 7.3	In Situ - IIIA	None CT only RT only CT + RT	None AOs AIs
Exercisers			**37**	**2.7**	**50 ± 9.5**	**81.3 ± 17.0**	**30.6 ± 6.0**			
Controls	Irwin et al. (2009) 12 month	USA	25	8	na	75.9 ± 17.7	na	In Situ - IIIA	None CT only RT only CT + RT	None AOs AIs
Exercisers			**25**	**0**	**na**	**81.2 ± 18.5**	**na**			
Controls	Rahnama et al. (2009)	Iran	16	6.25	50-65	70.17 ± 9.0	27.4 ± 3.4	I-IIIB	SUR + CT + RT	Current Hormone therapy Use
Exercisers			**16**	**12.5**	**50-65**	**70.4 ± 12.8**	**28.0 ± 4.7**			
Controls	Saarto et al. (2012)	Finland	131	9.2	58 (46-68)	70.0 ± 11.9	26.2 ± 4.2	I-IIIC	None CT only RT only CT + RT	None AOs AIs
Exercisers			**138**	**8.7**	**58 (48-68)**	**79.9 ± 12.5**	**27.2 ± 4.4**			
Controls	Winters-Stone et al. (2011)	USA	54	42.6	62.3 ± 6.7	74.0 ± 12.3	29.5 ± 5.6	In Situ - IIIA	None CT only RT only CT + RT	None AOs AIs
Exercisers			**52**	**30.8**	**62.2 ± 6.7**	**75.6 ± 15.5**	**29.5 ± 5.8**			

na = information not available; SUR = Surgery; CT = Chemotherapy, RT = Radiotherapy; AOs = Anti oestrogens; AIs = Aromatase Inhibitors

The attrition rate of exercisers ranged from 0% to 30.8% and the attrition rate of controls ranged from 6.25% to 42.6% (Table 11). Out of the 278 exercisers, 33 were lost to follow-up, therefore 245 completed exercise interventions and follow-up measurements. Out of the 274 controls, 46 were lost to follow-up, therefore 228 completed follow-up measurements.

The mean age of the participants ranged from 50 to 62 years (Table 11). The mean BM and BMI ranges were 66.7kg to 81.3kg and 24.0kg/m^2 to 30.6kg/m^2 respectively (Table 11). Studies included postmenopausal BCSs with in-situ to stage IIIC breast cancer (Table 11). Studies included BCSs who received a wide range of treatments from no treatment, to surgery, radiotherapy, chemotherapy, AIs, AOs or a combination (Table 11).

4.3. Exercise characteristics

All studies were conducted after the completion of primary treatment (surgery, radiotherapy, chemotherapy) and were conducted during the survivorship stage of the postmenopausal BCS experience (Table 12).

Three studies prescribed aerobic exercise in isolation (Irwin, Alvarez-Reeves, et al., 2009 [6 month & 12 month]; Saarto et al., 2012), one study prescribed resistance exercise in isolation (Winters-Stone et al., 2011) and two studies prescribed a combination of aerobic and resistance exercise (Herrero et al., 2006; Rahnama et al., 2010) (Table 12). Specific types of exercise included; walking, circuit training, cycling, step aerobics, weight lifting with fixed and free weights and impact jumping (Table 12).

Table 12

Characteristics of exercise interventions

Study	Timing	Type	Specific type	Frequency (days/week)	Time	Intensity	Duration (weeks)	Setting	Supervision	Adherence
Herrero et al., (2006)	AT	Aerobic and Resistance	Cycling Weight lifting	**3** 3x Cycling 3 x Weights	**Cycling** 20-30 min **Weights** 11 ex; 1-2 sets; 8-15 reps	70-80% max HR 8-15 rep max	8	RF	S	91% +-7%
Irwin et al. (2009) 6 month	AT	Aerobic	Walking	**5**	30min	60-80% max HR	26	RF+HM	S+UNS	73%
Irwin et al. (2009) 12 month	AT	Aerobic	Walking	**5**	30min	60-80% max HR	52	RF+HM	S+UNS	73%
Rahnama et al. (2009)	AT	Aerobic and Resistance	Walking Fixed and free weights	**4** 2 x Walking 2 x Weights	**Walking** 25-45 min **Weights** 9 ex; 3 sets; 10-14 reps	55-65% max HR 10-14 rep max	15	RF	S	na
Saarto et al. (2012)	AT	Aerobic	Step aerobics, circuit training, Walking	**3-4**	30-40min	14-16 RPE	52	RF+HM	S+UNS	S = 63% US = 107%*
Winters-Stone et al. (2011)	AT	Resistance	Free weights Resistance bands Impact jumping	**3**	**Weights**; 6-8 ex; 1-2 sets; 8-14 reps **Jumping**; 1-6 sets; 10 reps	**Weights** 0-15% BM 8-14 rep Max **Jumping** 0-10% BM	52	UN+HM	S+UNS	57% S = 76% US = 23%

na = information not available; AF = After Treatment; RF = Recreational Fitness; HM = Home; UNV = University; S = Supervised; UNS = Unsupervised

* exercise logs reported an average of 3.2 US exercise sessions a week, this was in excess of the prescribed 3 sessions therefore, adherence was >100%

The frequency of prescribed exercise ranged from three to five times a week. The time spent performing aerobic exercise ranged from 20 to 45min per session (Table 12). Resistance exercise was performed for six to eleven exercises, for eight to fifteen repetitions and for one to three sets per session (Table 12). Aerobic exercise intensity ranged from 55 to 80% of heart rate max and resistance exercise ranged from eight to fifteen repetition maximum (Table 12). The total duration of exercise interventions ranged from eight to fifty-two weeks (Table 12).

Five out of the six included studies used recreational fitness facilities as the setting (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 month & 12 month]; Rahnama et al., 2010; Saarto et al., 2012); three studies combined this with home based exercise (Irwin, Alvarez-Reeves, et al., 2009 [6 month & 12 month]; Saarto et al., 2012) and one study used a university research facility combined with home based exercise (Winters-Stone et al., 2011) (Table 12). Two studies included only supervised exercise (Herrero et al., 2006; Rahnama et al., 2010) whilst four studies used a combination of supervised and unsupervised exercise (Irwin, Alvarez-Reeves, et al., 2009 [6 month & 12 month]; Saarto et al., 2012; Winters-Stone et al., 2011) (Table 12).

Total adherence to the prescribed exercise ranged from 57% to 91% (Table 12). Adherence to supervised exercise ranged from 63% to 91% and adherence to unsupervised exercise ranged from 23% to 107% (Table 12).

4.4. BM and BMI outcomes

The effects of exercise on the BM and BMI of postmenopausal BCSs are presented in Table 13.

Table 13

Summary of the main effects of exercise on the BM and BMI of postmenopausal BCSs

Outcome	No of Studies	Study	Mean Change Controls	Mean Change Exercisers	Difference in Mean Change between Groups	P Value
BM (kg)	**6**	Herrero et al., (2006)	-0.40 kg	-1.10 kg	**-0.70 kg**	**p = >0.05**
		Irwin et al. (2009) 6 month	0.10 kg	-0.55 kg	**-0.65 kg**	**p = 0.39**
		Irwin et al. (2009) 12 month	0.65 kg	0.39 kg	**-0.26 kg**	**p = 0.61**
		Rahnama et al. (2009)	**1.43 kg**	**-0.99 kg**	**-2.42 kg**	**p = 0.031**
		Saarto et al. (2012)	0.15 kg	0.39 kg	**0.24 kg**	**p = 0.57**
		Winters-Stone et al. (2011)	0.2 kg	0.90 kg	**0.70 kg**	**p = 0.55**
BMI (kg/m^2)	**2**	Irwin et al. (2009) 6 month	0.16 kg/m^2	-0.12 kg/m^2	**-0.28 kg/m^2**	**p = 0.42**
		Rahnama et al. (2009)	**0.56 kg/m^2**	**-0.3 kg/m^2**	**-0.86 kg/m^2**	**p = 0.022**

Significant findings at the p =<0.05 level are highlighted in red

There was BM outcome data for all six studies (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 month & 12 month]; Rahnama et al., 2010; Saarto et al., 2012; Winters-Stone et al., 2011) (Table 13; Fig. 6).

In five out of the six included studies controls experienced mean gains in BM of 0.10kg (Irwin, Alvarez-Reeves, et al., 2009 [6 month]); 0.65kg (Irwin, Alvarez-Reeves, et al., 2009 [12 month]); 1.43kg (Rahnama et al., 2010); 0.15kg (Saarto et al., 2012) and 0.20kg (Winters-Stone et al., 2011); a mean loss in BM of 0.40kg was reported in one study (Herrero et al., 2006) (Table 13). In three studies exercisers experienced mean losses in BM of -1.1kg (Herrero et al., 2006); -0.55kg (Irwin, Alvarez-Reeves, et al., 2009 [6 month]) and -0.99kg (Rahnama et al., 2010). In the remaining three studies exercisers experienced mean gains in BM of 0.39kg (Irwin, Alvarez-Reeves, et al., 2009 [12 month]), 0.39kg (Saarto et al., 2012) and 0.90kg (Winters-Stone et al., 2011) (Table 13).

In four out of the six included studies exercisers either lost more BM, or did not gain as much BM, as controls with differences in mean change in BM between exercisers and controls of -0.70kg (Herrero et al., 2006); -0.65kg (Irwin, Alvarez-Reeves, et al., 2009 [6 month]); -0.26kg (Irwin, Alvarez-Reeves, et al., 2009 [12 month]) and -2.42kg (p=0.031) (Rahnama et al., 2010) (Table 13; Fig. 6). In the remaining two studies exercisers experienced greater increases in BM than controls, with differences in mean change in BM between exercisers and controls of 0.24kg (Saarto et al., 2012) and 0.70kg (Winters-Stone et al., 2011) (Table 13; Fig. 6). In one study exercise had a statistically significant beneficial effect on the BM of postmenopausal BCSs (Rahnama et al., 2010).

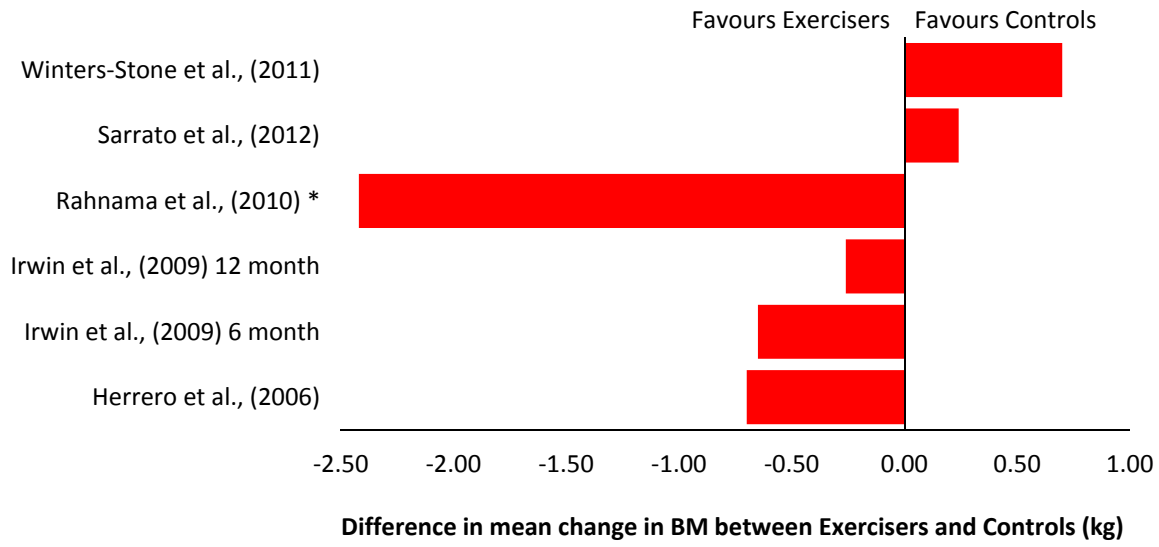

Figure 6

Difference in the mean change in BM (kg) between postmenopausal BCSs assigned to exercise and control conditions

There was BMI outcome data for two studies (Irwin, Alvarez-Reeves, et al., 2009 [6 month]; Rahnama et al., 2010) (Table 13; Fig. 7). Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported that controls increased their BMI by 0.16kg/m^2 whilst exercisers decreased their BMI by 0.12kg/m^2. Rahnama et al. (2010) reported that controls increased their BMI by 0.56kg/m^2 whilst exercisers decreased their BMI by 0.30kg/m^2. The differences in mean change in BMI between exercisers and controls were -0.28kg/m^2 (Irwin, Alvarez-Reeves, et al., 2009 [6 month]) and -0.86kg/m^2 (p=0.022) (Rahnama et al., 2010) (Table 13; Fig. 7).

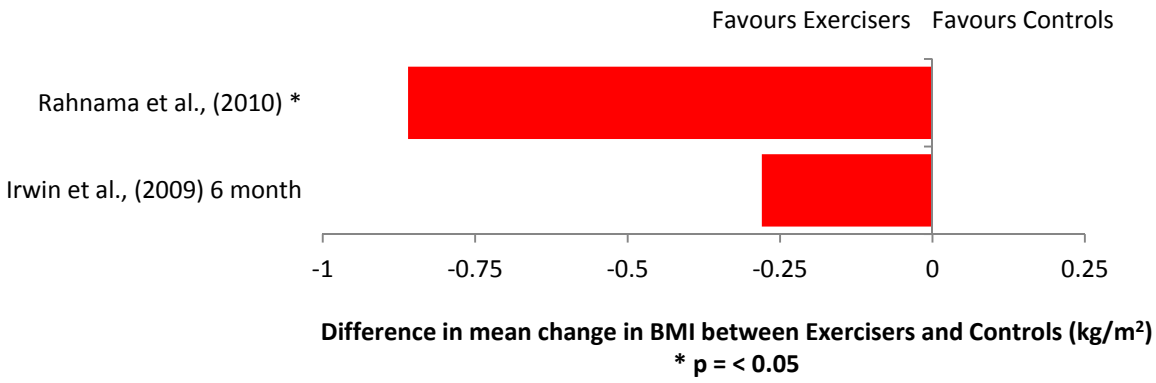

Figure 7

Difference in the mean change in BMI (kg/m^2) between postmenopausal BCSs assigned to exercise and control conditions

4.5. WC, LBM, FM and BF% outcomes

The main effects of exercise on the WC, LBM, FM and BF% of postmenopausal BCSs are presented in Table 14.

WC outcome data was available for two studies (Irwin, Alvarez-Reeves, et al., 2009 [6 month]; Rahnama et al., 2010) (Table 14; Fig. 8). Among controls Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported a mean reduction of -0.84cm and Rahnama et al. (2010) reported no mean change in WC. Among exercisers both Irwin, Alvarez-Reeves, et al. (2009) [6 month] and Rahnama et al. (2010) reported mean reductions in WC of -1.38cm and -3.0cm respectively. The differences in the mean change in WC between exercisers and controls were -0.54cm (Irwin, Alvarez-Reeves, et al., 2009 [6 month]) and -3.0cm (Rahnama et al., 2010) (Table 14; Fig 8). None of the WC findings were statistically significant.

Table 14

Summary of the effects of exercise on the WC, LBM, FM, and BF% of postmenopausal BCSs

Outcome		No of Studies	Study	Method of Body Composition Assessment	Mean Change Controls	Mean Change Exercisers	Difference in Mean Change between Groups	P Value
WC (cm)		**2**	Irwin et al. (2009) 6 month	Tape Measure	-0.84 cm	-1.38 cm	**-0.54 cm**	**p=0.57**
			Rahnama et al. (2009)	Tape Measure	0.00 cm	-3.00 cm	**-3.00 cm**	**na**
LBM (kg)	Muscle Mass	**5**	**Herrero et al., (2006)**	**3 site SKF***	**-0.30 kg**	**0.70 kg**	**1.00 kg**	**p=<0.05**
	LBM		**Irwin et al. (2009) 6 month**	**DEXA**	**-0.35 kg**	**0.34 kg**	**0.69 kg**	**p=0.047**
	LBM		Irwin et al. (2009) 12 month	DEXA	-0.09 kg	0.70 kg	**0.79 kg**	**p=0.25**
	LBM		Saarto et al. (2012)	DEXA	0.01 kg	0.34 kg	**0.33 kg**	**p=0.13**
	Bone free LBM		Winters-Stone et al. (2011)	DEXA	0.50 kg	0.60 kg	**0.10 kg**	**p = 0.91**
FM (kg)		**3**	Herrero et al., (2006)	3 site SKF**	0.00 kg	-1.70 kg	**-1.70 kg**	**p = >0.05**
			Saarto et al. (2012)	DEXA	0.50 kg	0.48 kg	**-0.02 kg**	**p = 0.95**
			Winters-Stone et al. (2011)	DEXA	0.00 kg	0.50 kg	**0.50 kg**	**p = 0.50**
BF% (%)		**4**	**Herrero et al., (2006)**	**3 site SKF****	**0.00 %**	**-2.00 %**	**-2.00 %**	**p=<0.05**
			Irwin et al. (2009) 6 month	**DEXA**	**0.42 %**	**-0.79 %**	**-1.21 %**	**p=0.0022**
			Irwin et al. (2009) 12 month	**DEXA**	**-0.03 %**	**-1.19 %**	**-1.16 %**	**p = 0.043**
			Winters-Stone et al. (2011)	DEXA	-0.20 %	0.00 %	**0.20 %**	**p = 0.51**

Significant findings at the p = <0.05 level are highlighted in red

* using anthropometrical data and the equations of Lee et al. (2000); ** using the equations of Jackson and Pollock (1985)

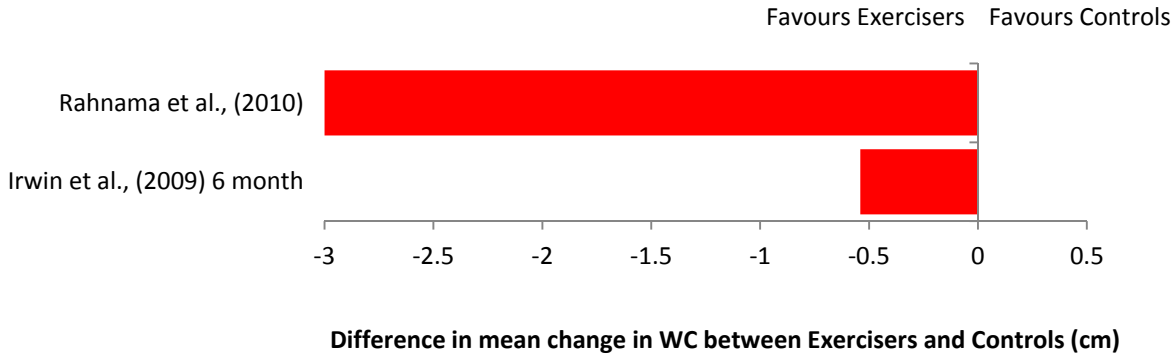

Figure 8

Difference in the mean change in WC (cm) between postmenopausal BCSs assigned to exercise and control conditions

LBM outcome data was available for five studies (Table 14; Fig. 9). In three studies controls experienced mean losses in LBM of; -0.30 (Herrero et al., 2006); -0.35kg (Irwin, Alvarez-Reeves, et al., 2009) [6 month] and -0.09 (Irwin, Alvarez-Reeves, et al., 2009) [12 month]. In two studies controls experienced mean gains in LBM of; 0.01kg (Saarto et al., 2012) and 0.50kg (Winters-Stone et al., 2011). In all five studies exercisers experienced mean gains in LBM of; 0.70kg (Herrero et al., 2006); 0.34kg (Irwin, Alvarez-Reeves, et al., 2009) [6 month]; 0.70kg (Irwin, Alvarez-Reeves, et al., 2009) [12 month]; 0.34kg (Saarto et al., 2012) and 0.60kg (Winters-Stone et al., 2011) (Table 14). The difference in mean change in LBM between exercisers and controls favoured exercisers in all five studies; 1.00kg (Herrero et al., 2006); 0.69kg (Irwin, Alvarez-Reeves, et al., 2009 [6 month]); 0.79kg (Irwin, Alvarez-Reeves, et al., 2009 [12 month]); 0.33kg (Saarto et al., 2012) and 0.10kg (Winters-Stone et al., 2011) (Table 14; Fig. 9). In two studies exercise had a statistically significant beneficial effect on

the LBM of postmenopausal BCSs of 1.0kg (p=<0.05) and 0.69kg (p=0.047) respectively (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 month]).

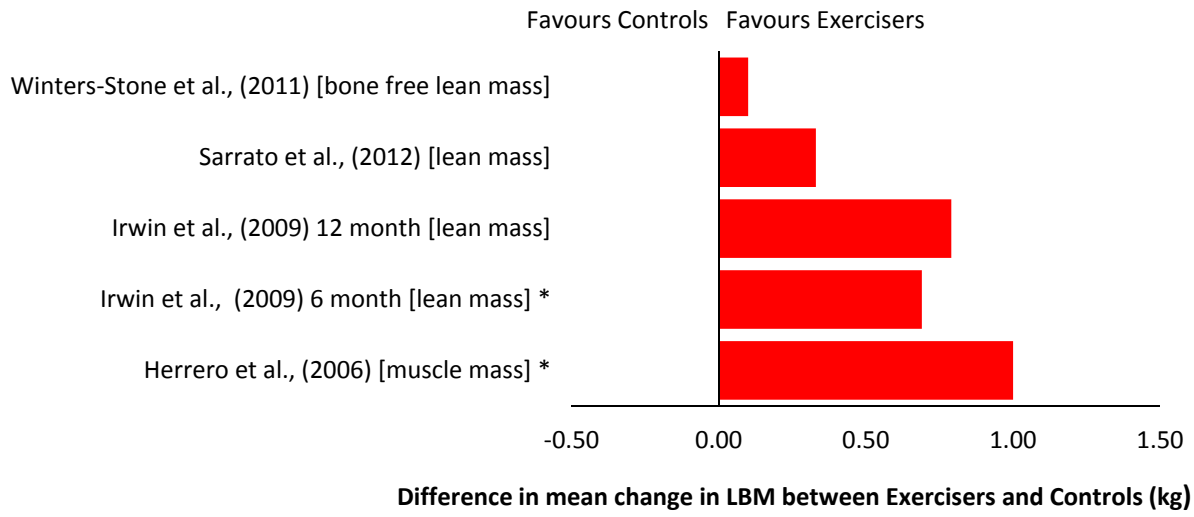

Figure 9

Difference in the mean change in LBM (kg) between postmenopausal BCSs assigned to exercise and control conditions

FM outcome data was available for three studies (Herrero et al., 2006; Saarto et al., 2012; Winters-Stone et al., 2011) (Table 16; Fig. 10). Controls either experienced no mean change in FM, (Herrero et al., 2006; Winters-Stone et al., 2011) or a mean gain of 0.50kg (Saarto et al., 2012). Among exercisers one study reported a mean reduction in FM of -1.70kg (Herrero et al., 2006) and two studies reported mean FM gains of 0.48kg (Saarto et al., 2012) and 0.50kg (Winters-Stone et al., 2011). The differences in mean change in FM between exercisers and controls were -1.7kg (Herrero et al., 2006); -0.02kg (Saarto et al., 2012) and 0.50kg (Winters-Stone et al., 2011) (Table 14; Fig. 10). None of the FM findings were statistically significant.

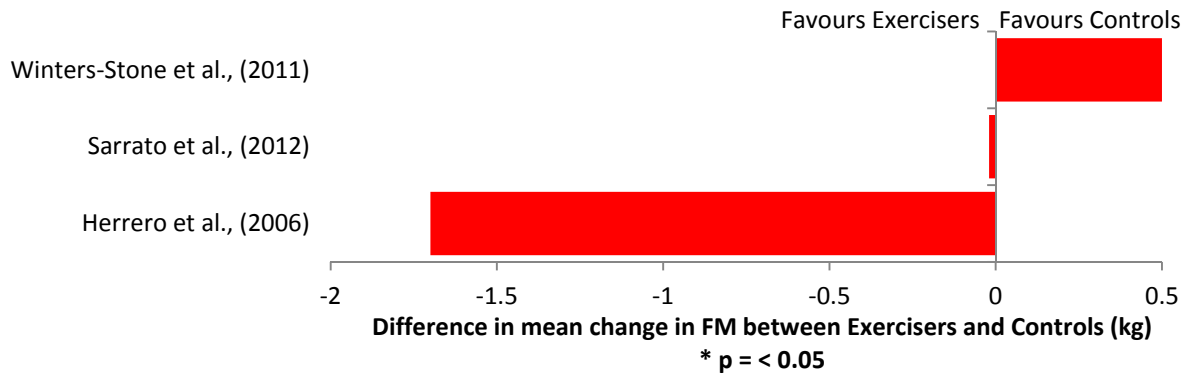

Figure 10

Difference in the mean change in FM (kg) between postmenopausal BCSs assigned to exercise and control conditions

BF% outcome data was available for four studies (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]; Winters-Stone et al., 2011) (Table 14; Fig. 11). Among controls; Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported a mean increase in BF% of 0.42%; Herrero et al. (2006) reported no mean change in BF% and Irwin, Alvarez-Reeves, et al. (2009) [12 month] and Winters-Stone et al. (2011) reported small mean reductions in BF% of -0.03% and -0.20% respectively. Among exercisers Herrero et al. (2006) and Irwin, Alvarez-Reeves, et al. (2009) [6 & 12 month] reported mean reductions in BF% of -2.00%; 0.79% and -1.19% respectively, and Winters-Stone et al. (2011) reported no mean change in BF% (Table 16). The differences in the mean change in BF% between exercisers and controls were -2.00% (p=<0.05) (Herrero et al., 2006), -1.21% (p=0.0022) (Irwin, Alvarez-Reeves, et al., 2009 [6 month]); -1.16% (p=0.043) (Irwin, Alvarez-Reeves, et al., 2009 [12 month]) and 0.20% (Winters-Stone et al., 2011) (Table 14; Fig 11). Three out of four studies reported that exercise had a statistically significant beneficial effect on the BF%

of postmenopausal BCSs (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]) (Table 14; Fig 11).

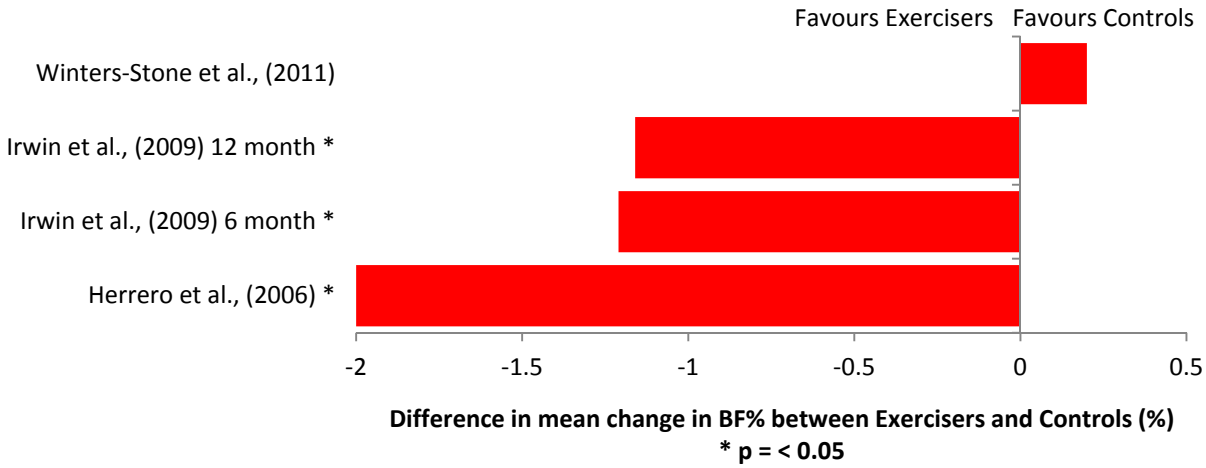

Figure 11

Difference in the mean change in BF% between postmenopausal BCSs assigned to exercise and control conditions

4.6. BMC and BMD Outcomes

The main effects of exercise on the BMC and BMD of postmenopausal BCSs are presented in Table 15.

BMC outcome data was available for three studies (Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]; Saarto et al., 2012) (Table 15; Fig. 12). Among controls Irwin, Alvarez-Reeves, et al. (2009) [12 month] and Saarto et al. (2012) reported mean reductions in BMC of -66g/cm and -49g/cm respectively; whilst Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported a mean increase of 2g/cm. Among exercisers Irwin, Alvarez-Reeves, et al. (2009) [6 month] and Saarto et al. (2012) reported mean reductions in BMC of -44g/cm and -60g/cm respectively; whilst Irwin, Alvarez-Reeves, et al. (2009) [12 month] reported a mean increase of 2g/cm (Table 15).

Table 15

Summary of the main effects of exercise on the BMC and BMD of postmenopausal BCSs

Outcome	Specific Site	No of Studies	Study	Method of Body Composition Assessment	Mean Change Controls	Mean Change Exercisers	Difference in Mean Change between Groups	P Value
BMC (g/cm)	**Total**	**3**	Irwin et al. (2009) 6 month	DEXA	2	-44	**-46**	**p = 0.062**
			Irwin et al. (2009) 12 month	DEXA	-66	2	**68**	**p = 0.13**
			Saarto et al. (2012)	DEXA	-49	-60	**-11**	**p = 0.25**
BMD (g/cm^2)	**Total**	**4**	Irwin et al. (2009) 6 month	DEXA	-0.008	-0.008	**0.000**	**p = 0.97**
	Total		**Irwin et al. (2009) 12 month**	**DEXA**	**-0.025**	**0.008**	**0.033**	**p = 0.043**
	Lumbar Spine		Sarrarto et al. (2012)	DEXA	-0.020	-0.016	**0.004**	**p = 0.30**
	Lumbar Spine (L1-L4)		**Winters-Stone et al. (2011)**	**DEXA**	**-0.022**	**0.004**	**0.026**	**p = <0.01**
	Femoral Neck		Saarto et al. (2012)	DEXA	-0.010	-0.010	**0.000**	**p = 0.99**
	Femoral Neck		Winters-Stone et al. (2011)	DEXA	-0.015	-0.010	**0.005**	**p = 0.27**
	Greater Trochanter		Winters-Stone et al. (2011)	DEXA	-0.001	-0.003	**-0.002**	**p = 0.15**
	Total Hip		Winters-Stone et al. (2011)	DEXA	-0.007	-0.003	**0.004**	**p = 0.13**

Significant findings at the p =<0.05 level are highlighted in red

The differences in the mean change in BMC between exercisers and controls were -46g/cm (Irwin, Alvarez-Reeves, et al., 2009 [6 month]), 68g/cm (Irwin, Alvarez-Reeves, et al., 2009 [12 month]) and -11g/cm (Saarto et al., 2012) (Table 15; Fig. 12). None of the BMC findings were statistically significant.

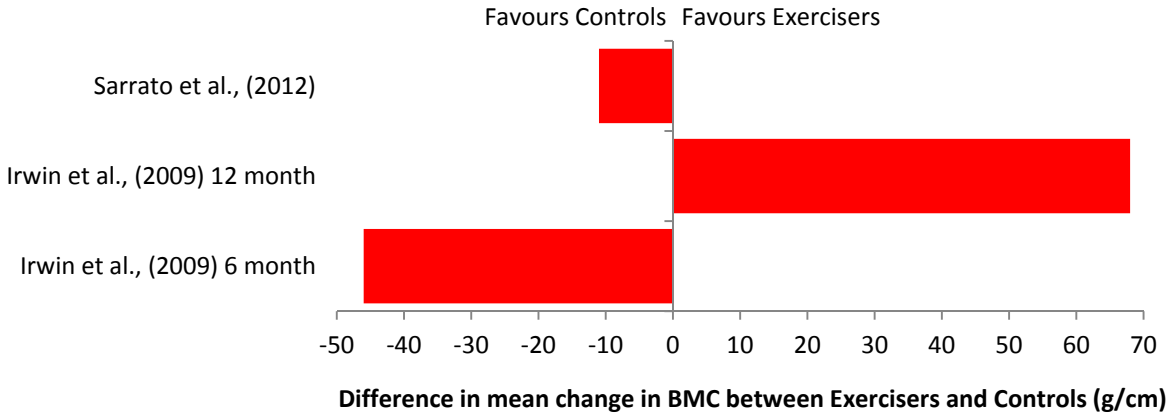

Figure 12

Difference in the mean change in BMC (g/cm) between postmenopausal BCSs assigned to exercise and control conditions

Total BMD outcome data was available in two cases; both outcomes were from the same study (Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]) (Table 15; Fig. 13). Among the 6 month subset, both exercisers and controls experienced a mean reduction in total BMD of -0.008g/cm^2, therefore there was no mean difference in total BMD between exercisers and controls (Irwin, Alvarez-Reeves, et al., 2009 [6 month]). Among the twelve month subset the mean change in total BMD of controls was -0.025g/cm^2 and was 0.008g/cm^2 among exercisers, therefore the mean difference in total BMD between exercisers and controls was 0.033g/cm^2 (p=0.043). In one study exercise had a statistically significant

beneficial effect on the total BMD of postmenopausal BCSs (Irwin, Alvarez-Reeves, et al., 2009 [12 month]) (Table 15; Fig. 13).

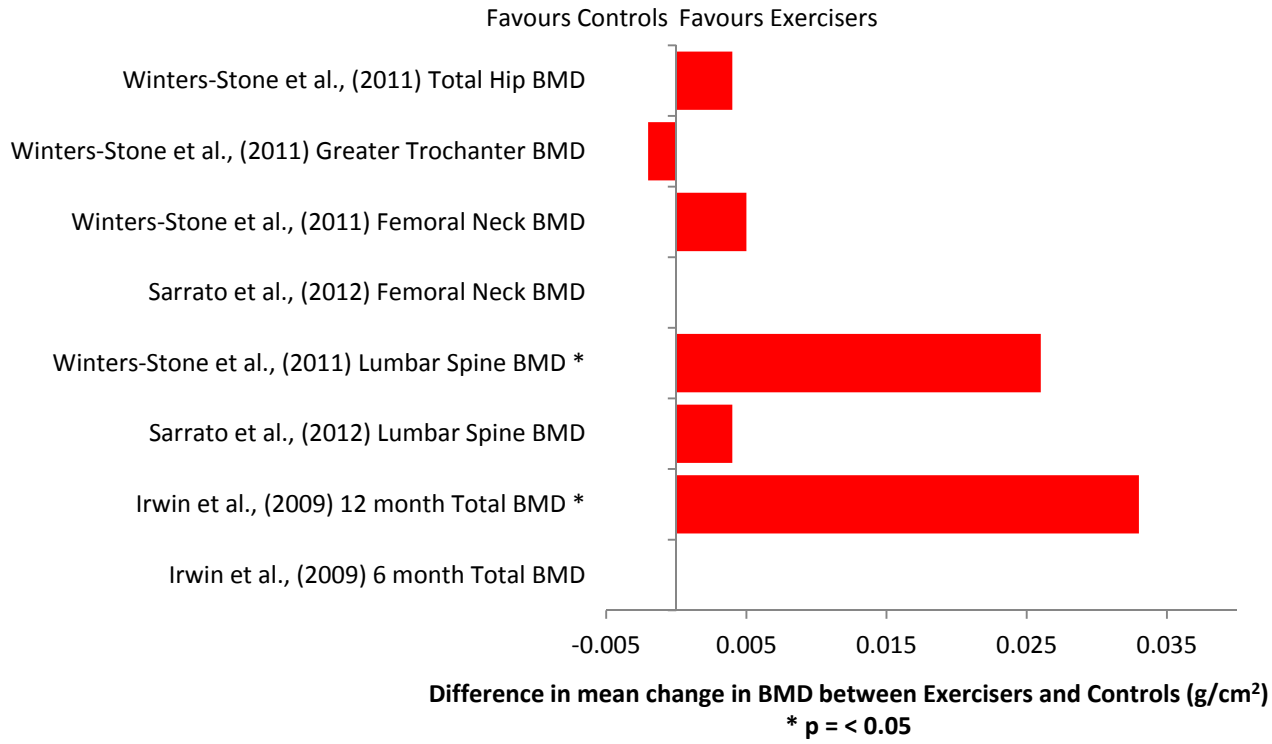

Figure 13

Difference in the mean change in BMD (g/cm^2) between postmenopausal BCSs assigned to exercise and control conditions

Lumbar spine BMD was an outcome in two studies (Saarto et al., 2012; Winters-Stone et al., 2011) (Table 15; Fig. 13). Saarto et al. (2012) reported that control and exercise groups both experienced mean reductions in lumbar spine BMD of -0.020g/cm^2 and -0.016g/cm^2 respectively, therefore the difference in mean change between exercisers and controls was 0.004g/cm^2. Among controls Winters-Stone et al. (2011) reported a mean reduction in lumbar spine BMD of -0.022g/cm^2 and a mean gain of 0.004g/cm^2 among exercisers; the difference in mean change between exercisers and controls was

0.026g/cm^2 (p=<0.01) (Table 15; Fig. 13). In one study exercise had a statistically significant beneficial effect on the lumbar spine BMD of postmenopausal BCSs (Winters-Stone et al., 2011).

Femoral neck BMD was an outcome in two studies (Saarto et al., 2012; Winters-Stone et al., 2011) (Table 15; Fig. 13). In both studies controls experienced mean reductions in femoral neck BMD of; -0.010g/cm^2 (Saarto et al., 2012) and -0.015g/cm^2 (Winters-Stone et al., 2011). Both exercise groups also experienced mean reductions in femoral neck BMD of; -0.010g/cm^2 (Saarto et al., 2012) and -0.010g/cm^2 (Winters-Stone et al., 2011). Therefore the differences in mean change between exercisers and controls were 0.00g/cm^2 (Saarto et al., 2012) and 0.005g/cm^2 (Winters-Stone et al., 2011) (Table 15; Fig. 13). None of the femoral neck BMD findings were statistically significant.

BMD outcome data was available for two additional sites from one study (Winters-Stone et al., 2011). Winters-Stone et al. (2011) reported that both controls and exercisers experienced mean reductions in greater trochanter BMD of -0.001g/cm^2 and -0.003g/cm^2 respectively; the loss was less pronounced among controls, and the difference in mean change in greater trochanter BMD between exercisers and controls was -0.002g/cm^2 (Table 15; Fig. 13). Both controls and exercisers also experienced mean reductions in total hip BMD of -0.007g/cm^2 and -0.003g/cm^2 respectively; the loss was less pronounced among exercisers and the difference in mean change in total hip BMD between exercisers and controls was 0.004g/cm^2 (Winters-Stone et al., 2011) (Table 15; Fig. 13). The differences in greater trochanter BMD and total hip BMD between exercisers and controls were not statistically significant.

4.7. Risk of bias within studies

The results of the assessment of the methodological quality and risk of bias for studies included in the review are presented in Table 16.

Table 16

Downs and Black Checklist (1998) subtotal and total percentage score for studies included in the systematic review

	Herrero et al., (2006)	Irwin et al. (2009)	Rahnama et al., (2009)	Sarrto et al., (2012)	Winters-Stone et al., (2011)
Reporting Subtotal (%)	**73%**	**91%**	**73%**	**91%**	**100%**
External Validity Subtotal (%)	**33%**	**67%**	**67%**	**67%**	**33%**
Internal Validity (Bias) Subtotal (%)	**86%**	**86%**	**71%**	**86%**	**74%**
Internal Validity (Selection Bias) Subtotal (%)	**83%**	**100%**	**50%**	**83%**	**100%**
Power Subtotal (%)	**100%**	**100%**	**100%**	**100%**	**100%**
Total Score (%)	**78%**	**91%**	**72%**	**88%**	**88%**

Downs and Black Checklist (1998) reporting subtotal percentage scores ranged from 73% to 100%; external validity subtotal percentage scores ranged from 33% to 67%; internal validity (bias) subtotal percentage scores ranged from 71% to 86% and internal validity (section bias) subtotal percentage scores ranged from 50% to 100% (Table 16). All studies scored the maximum available on the Downs and Black Checklist (1998) power subtotal with

percentage scores of 100% (Table 16). The total methodological quality of individual studies was high; with Downs and Black Checklist (1998) total percentage scores of 78% (Herrero et al., 2006), 91% (Irwin, Alvarez-Reeves, et al., 2009); 72% (Rahnama et al., 2010); 88% (Saarto et al., 2012) and 88% (Winters-Stone et al., 2011) (Table 16).

The study of Irwin, Alvarez-Reeves, et al. (2009) obtained the highest overall score; and scored highest or equal highest in all of the subtotal areas. The study of Rahnama et al. (2010) obtained the lowest overall score; and scored lowest or equal lowest in all of the subtotal areas (Table 16).

4.8. Risk of bias across studies: language bias

The search strategy returned a total of 226 non-English language records, of those 14 met the initial eligibility criteria. Although it was not possible to assess non-English language records against the full eligibility criteria, as full text articles were not available in the English language, in order to assist future researchers a list of non-English language studies meeting the initial eligibility criteria is attached in Appendix 20.

5.0. Discussion

5.1. Characteristics of the participants included in the final review

The total number of postmenopausal BCSs exposed to exercise interventions and included in this review was 278; after accounting for attrition this fell to 245. The attrition rates of individual studies were generally acceptable, and attrition was equally distributed amongst exercisers and controls (Table 11). This suggests that postmenopausal BCSs found exercise participation acceptable. However Winters-Stone et al. (2011) reported high attrition rates among controls and exercisers of 42.6% and 30.8% respectively (Table 11). Similar reasons for attrition were given by controls and exercisers, and the primary reason was that participants were "too busy". As only four participants stated that attrition was due to "poor health" it is unlikely that worsening health confounded the results in this study (Winters-Stone et al., 2011).

Past research that has included older, overweight and obese postmenopausal BCSs, has been limited (Visovsky, 2006). The inclusion of older, overweight and obese postmenopausal BCSs (mean age range 50 to 62 years; mean BMI range 24.0kg/m^2 to 30.6kg/m^2; Table 11) is a strength this review. However, postmenopausal BCSs with stage 4 breast cancer were not included and research amongst postmenopausal BCSs with higher disease stages is lacking (Table 11). Only Irwin, Alvarez-Reeves, et al. (2009) reported the ethnicity of the participants; and 84% of BCSs were Non-Hispanic White. In the future researchers should report ethnicity, and include BCSs from more diverse ethnic backgrounds and with higher disease stages.

The relatively low number of participants included in this review means that external validity may have been compromised, and the generalisation of

findings to the entire postmenopausal BCS population may be limited. In the future researchers should seek to increase the total number of postmenopausal BCSs recruited into exercise intervention studies. This would allow results to be stratified in relation to key confounders such as age, ethnicity, baseline BMI, breast cancer disease stage and type of treatment without statistical power being compromised.

5.2. Characteristics of the exercise interventions included in the final review

All of the exercise interventions included in this review were conducted after the completion of primary treatment (Table 12). As Del Rio et al. (2002) and Genton et al. (2006) reported that BM gain can occur during treatment, studies that examine the effect of exercise during treatment are warranted.

A variety of different types of exercise were included in this review; including aerobic exercise (Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]; Saarto et al., 2012), resistance exercise (Winters-Stone et al., 2011) and aerobic and resistance exercise in combination (Herrero et al., 2006; Rahnama et al., 2010). Activities included walking, circuit training, cycling, step aerobics, weight lifting with fixed and free weights and impact jumping (Table 12). Herrero et al. (2006); Irwin, Alvarez-Reeves, et al. (2009) [6 & 12 month]; Saarto et al. (2012) and Winters-Stone et al. (2011) all specifically reported that that no adverse events occurred in response to exercise; Rahnama et al. (2010) did not report this information. It therefore appears that a wide variety of exercises can be performed safely by older, overweight and obese postmenopausal BCSs. This review adds to the growing body of evidence which indicates that exercise can

be performed safely by cancer survivors (A. Campbell et al., 2011; Hayes et al., 2009; Macmillan Cancer Support, 2012; Schmitz et al., 2010).

Irwin, Alvarez-Reeves, et al. (2009) [6 &12 month] and Winters-Stone et al. (2011) both reported that EI did not change from baseline over the course of the exercise interventions, either among controls or exercisers. This suggests any beneficial effects on BM and body composition reported by these studies were likely to be due to increased EE from exercise, rather than dietary reductions in EI. However Herrero et al. (2006) Rahnama et al. (2010) and Saarto et al. (2012) did not report EI; therefore it was not possible to determine if any beneficial BM and body composition changes were due to increased in EE from exercise, or due to dietary reductions in EI. To enable the causes of BM and body composition change to be elucidated future researchers should include a measure of EI.

A strength of this review was the use of a HQTS Tool to determine study eligibility (Appendix 13) (Markes, 2010). As a result only exercise interventions with frequencies, intensities, times and total durations that were likely to induce beneficial BM and body composition adaptations were included in the final review (Table 12). However in order to be effective an exercise intervention must be adhered to.

Total exercise adherence was generally acceptable, and Herrero et al. (2006) reported a mean exercise adherence of 91% (Table 12). However the study of Winters-Stone et al. (2011) was a notable exception, and a mean exercise adherence of 57% (supervised=76%; unsupervised=26%) was reported (Table 12). The low adherence in the Winters-Stone et al. (2011) study may have been due to; the long total exercise duration, the university setting or the use of free

weights and impact jumping; these characteristics may have been off-putting or unappealing to postmenopausal BCSs. In contrast Saarto et al. (2012) reported an unsupervised exercise adherence of 107%; the figure of 107% is valid, as according to exercise logs BCSs performed an average of 3.2 unsupervised exercise sessions a week, this was in excess of the prescribed 3 sessions a week, therefore exercise adherence was in excess of 100%. It is possible that these postmenopausal BCSs were highly motivated to exercise, however it is more likely that over-estimates of self-reported PA were responsible. Irwin, Alvarez-Reeves, et al. (2009) reported a mean exercise adherence of 73%; however postmenopausal BCSs with the greatest exercise adherence achieved the greatest beneficial body composition changes.

The importance of exercise adherence cannot be overstated, as in order for the potential benefits of exercise to be imparted to postmenopausal BCSs, exercise must actually be performed and maintained. Two recent studies have indicated that CBT, and brief regular contact in the form of newsletters and telephone counselling, can increase adherence to a healthy lifestyle and result in beneficial body composition changes among; older, overweight and obese cancer survivors (Demark-Wahnefried et al., 2012); and overweight BCSs (Mefferd, Nichols, Pakiz, & Rock, 2007). A research protocol with the aim of improving exercise adherence in cancer survivors has recently been published (Rogers et al., 2012). This is an area of research which demands further study.

5.3. Methods of body composition assessment included in the final review

DEXA is considered a valid and reliable method of body composition assessment (Heyward & Wagner, 2004, pp. 40-44). Therefore the fact that Irwin, Alvarez-Reeves, et al. (2009) [6 & 12 month], Saarto et al. (2012) and Winters-Stone et al. (2011) used DEXA as the primary method of body composition assessment is a strength of this review (Table 14). Mefferd et al. (2007) reported that, among a small sample of 76 BCSs (84% postmenopausal), WC and BMI were strongly related to BF% measured by DEXA (WC; r=0.579; p=<0.01; BMI; r=0.596; p=<0.01) and to trunk fat measured by DEXA (WC; r=0.86, p=<0.01; BMI; r=0.82, p=<0.01). However Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported that significant increases in LBM and BF% occurred in postmenopausal BCSs, without any significant change in BMI or WC (Tables 13 & 14). Therefore the use of combined BMI and WC measurements may overlook important body composition changes in postmenopausal BCSs, who may experience atypical sarcopenic BM gain. Battaglini et al. (2011) and Freedman et al. (2004) have reported that common methods of body composition assessment may not be valid in BCS populations. And due to the expense and lack of accessibility DEXA can only feasibly be used for research purposes, and is unsuitable for use with larger sample sizes (Heyward & Wagner, 2004, pp. 40-44). Therefore there is a need to develop simple, inexpensive methods of body composition assessment that are validated in the specific postmenopausal BCS population. This would enable body composition to be monitored in community health and fitness settings, and enable larger sample sizes to be used in research.

5.4. The effects of exercise on the BM and BMI of postmenopausal BCSs

Both Irwin, Alvarez-Reeves, et al. (2009) [6 month] and Rahnama et al. (2010) found that exercise had a favourable effect on the BMI of postmenopausal BCSs (Table 13; Fig. 7). The findings from four out of the six included studies indicated exercise had a favourable effect on the BM of postmenopausal BCSs (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]; Rahnama et al., 2010); the remaining two studies favoured control conditions (Saarto et al., 2012; Winters-Stone et al., 2011) (Table 13; Fig. 6). However, the two studies that favoured control conditions had methodological flaws. The study of Winters-Stone et al. (2011) had poor exercise adherence; therefore the stimulus provided by exercise may not have been sufficient to reduce BM. The control group in the Saarto et al. (2012) study spontaneously increased their PA, therefore any beneficial effect of exercise may have been obscured. These methodological flaws may have influenced other body composition outcomes from these two studies and this should be considered when analysing other results.

Apart from the study of Rahnama et al. (2010), no other included study found any statistically significant effect of exercise on the BM or BMI of postmenopausal BCSs. In all other studies, the differences in mean change in BM between exercisers and controls were less than 1kg, and were therefore unlikely to be clinically important (Table 13; Fig. 6). Rahnama et al. (2010) reported statistically significant differences in mean change in BM and BMI between exercisers and controls of -2.42kg ($p=0.031$) and -0.86kg/m^2 ($p=0.022$) respectively (Table 13; Figs. 6 & 7). However, a mean difference of <1.0 BMI

point is unlikely to result in a reclassification of BMI status, therefore although these differences may be statistically significant they are unlikely to be clinically significant. Especially as of the -0.86kg/m^2 difference in mean change in BMI between exercisers and controls reported by Rahnama et al. (2010), 0.56kg/m^2 was attributed to a mean gain among controls, and -0.30kg/m^2 was attributed to a mean loss among exercisers (Table 13). Herrero et al. (2006) reported that exercising postmenopausal BCSs lost a mean BM of -1.1kg, this was the greatest mean BM loss among exercisers of any of the included studies; however as controls lost a mean of -0.40kg, the difference in mean change in BM between exercisers and controls was -0.70kg (Table 13; Fig. 6).

The two studies that reported the greatest beneficial effects of exercise on BM were the only two studies included in this review to prescribe a combination of aerobic and resistance exercise (Herrero et al., 2006; Rahnama et al., 2010) (Tables 12 & 13; Fig. 6). These two studies also had the shortest total exercise durations; of 8 weeks (Herrero et al., 2006) and 15 weeks (Rahnama et al., 2010) as opposed to the 26 or 52 week durations of the remaining studies (Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]; Saarto et al., 2012; Winters-Stone et al., 2011). If the BM reductions that occurred in response to combined aerobic and resistance exercise continued at the same rate, and if exercise adherence could be maintained, increased total exercise durations of this type of exercise may have the potential to produce clinically significant reductions in the BM and BMI of postmenopausal BCSs.

Only the study of Rahnama et al. (2010) demonstrated a statistically significant effect of exercise on BM and BMI. However this study had the greatest risk of bias of all the studies included in this review; and had the lowest; internal

validity-bias (71%), internal validity-selection bias (50%) and total methodological quality (72%) scores (Table 16). Therefore the findings from the Rahnama et al. (2010) study were the most likely, out of all the included studies, to be subject to an exaggerated treatment effect. However, the statistically significant effect of exercise on BM and BMI reported by Rahnama et al. (2010) may have been related to a particular characteristic of the exercise intervention used. For example, Rahnama et al. (2010) required that all exercise sessions be supervised; it is possible that this supervision resulted in higher adherence and greater effort during exercise among postmenopausal BCSs.

The findings from this review indicate that some exercise prescriptions have the potential to attenuate BM gain and induce small reductions in the BM of postmenopausal BCSs, during the recovery and survivorship stages of the breast cancer experience. Further research utilising combined aerobic and resistance exercise over longer total exercise durations is warranted.

5.5. The effects of exercise on the WC of postmenopausal BCSs

Both Irwin, Alvarez-Reeves, et al. (2009) [6 month] and Rahnama et al. (2010) found that exercise had a favourable effect on the WC of postmenopausal BCSs (Table 14; Fig. 8). At baseline, the mean WC of the exercise groups were 91.13cm (Irwin, Alvarez-Reeves, et al., 2009 [6 month]) and 99.0cm (Rahnama et al., 2010) (Table 14). These mean WC were >88cm, meaning a significant number of participants were at a significantly increased risk of obesity related diseases (National Institute for Health and Clinical Excellence, 2006; World Health Organisation, 2004). After 26 weeks of aerobic exercise

Irwin, Alvarez-Reeves, et al. (2009) reported a mean reduction in WC of -1.38cm to 89.75cm (Table 14). After 15 weeks of aerobic and resistance exercise Rahnama et al. (2010) reported a mean reduction in WC of -3.0cm to 96.0cm (Table 14). The findings of Rahnama et al. (2010) are in agreement with those of Cheema and Gaul (2006) who reported a mean reduction in WC of 2.8cm among a largely postmenopausal sample of BCSs after eight weeks of combined aerobic and resistance exercise.

From the limited studies available, it appears that if combined aerobic and resistance exercise were to be maintained over the longer term, and if reductions in WC were maintained at the same rate, this type of exercise has the potential to result in the reclassification of the risk of obesity related diseases. For example, if the postmenopausal BCSs in the Rahnama et al. (2010) study continued to exercise for a further 45 weeks, mean WC could be reduced by a further 9cm to 87cm; thus a significant number of participants could significantly reduce their risk of obesity related diseases. However this is only a theoretical assumption, and only further research where the total duration of the exercise period was extended, would reveal if this were actually the case.

5.6. The effects of exercise on the LBM, FM and BF% of postmenopausal BCSs

LBM was an outcome in five studies; all these studies found exercise had a favourable effect on the LBM of postmenopausal BCSs (Table 14; Fig. 9). The findings from three studies indicated that exercisers gained LBM, whilst controls lost LBM (Herrero et al., 2006; Irwin, Alvarez-Reeves, et al., 2009 [6 & 12 month]). Herrero et al. (2006) and Irwin, Alvarez-Reeves, et al. (2009) reported

statistically significant beneficial effects of exercise on the LBM of postmenopausal BCSs; with differences in mean change in LBM between exercisers and controls of 1.0kg (p=<0.05) and 0.69kg (p=0.047) respectively (Table 14; Fig. 9).

The findings of Herrero et al. (2006) and Irwin, Alvarez-Reeves, et al. (2009) [6 month] are encouraging; as exercise resulted in mean LBM gains, even in the face of mean reductions in BM (Tables 13 & 14; Figs. 6 & 9). These findings suggest that exercise was able to counteract the sarcopenic BM gain that some postmenopausal BCSs experience during the treatment and recovery stages of the BCS experience. However, it is important to note that Herrero et al. (2006) measured muscle mass (which excludes bone mass) and Irwin, Alvarez-Reeves, et al. (2009) [6 month] measured LBM (which includes bone mass) therefore these findings are not directly comparable (Table 14).

FM was an outcome in three studies; the findings from two of these studies indicated that exercise had a favourable effect on the FM of postmenopausal BCSs (Table 14; Fig. 10). Herrero et al. (2006) reported a mean reduction in FM among exercisers of 1.70kg and no change in FM among controls. Saarto et al. (2012) reported a minimal difference in mean FM change of 0.02kg in the favour of exercisers. Winters-Stone et al. (2011) reported that control conditions were favoured, as exercisers gained 0.50kg of FM whereas controls experienced no mean change in FM (Table 14; Fig. 10). Exercisers in the Winters-Stone et al. (2011) study also gained BM and LBM (Tables 13 & 14); suggesting that the BM gains of these postmenopausal BCSs were of the type typically seen in healthy women, as opposed to the sarcopeinc BM gains that have been observed among some BCSs.

BF% was an outcome in four included studies (Table 14; Fig.11). Winters-Stone et al. (2011) reported that control conditions were favoured, as the BF% of exercisers remained stable, whilst controls lost a mean BF% of 0.20% (Table 14; Fig. 11). Herrero et al. (2006) and Irwin, Alvarez-Reeves, et al. (2009) [6 & 12 month] all reported a statistically significant favourable effect of exercise on the BF% of postmenopausal BCSs (Table 14; Fig 11). The greatest reduction in BF% was reported by Herrero et al. (2006), who reported that exercisers experienced a mean reduction in BF% of -2.0%, whilst no mean change in BF% was observed among controls (p=<0.05) (Table 14; Fig 11).

The findings of Irwin, Alvarez-Reeves, et al. (2009) [6 and 12 month] suggest that performing aerobic exercise over a longer total exercise duration may result in greater body composition benefits among postmenopausal BCSs. Compared to BCSs who exercised for 6 months, BCSs who exercised for 12 months experienced greater mean increases in LBM (0.34kg vs. 0.70kg), and greater mean reductions in BF% (-0.79% vs. -1.19%) (Table 14; Figs. 9 & 11).

Herrero et al. (2006) and Irwin, Alvarez-Reeves, et al. (2009) [6 and 12 month] reported a statistically significant beneficial effect of exercise on the LBM and BF% of postmenopausal BCSs; despite not reporting any statistically significant effect of exercise on BM or BMI (Tables 13 & 14). These findings are in agreement with those of Cheema and Gaul (2006), Courneya et al. (2003) and Matthews et al. (2007). Both Courneya et al. (2003) and Cheema and Gaul (2006) reported mean reductions in the sum of SKFs, with no mean change in BM or BMI, among exercising postmenopausal BCSs. Matthews et al. (2007) reported that after 12 weeks of a counselling intervention, designed to promote walking among postmenopausal BCSs, there was no significant change in

mean BM; however there was a trend towards increased LBM and reduced FM and BF% among exercising postmenopausal BCSs.

The findings of this review suggest that exercise can induce beneficial changes in the LBM, FM and BF% of postmenopausal BCSs, independent of any change in BM or BMI. This is in agreement with previous reviews of BCS populations with mixed menopausal statuses (Cheema et al., 2008; Ingram et al., 2006; Kim et al., 2009; Stevinson et al., 2004; White et al., 2009).

5.7. The effects of exercise on the BMC and BMD of postmenopausal BCSs

Findings from the studies included in this review show a mixed effect of exercise on the BMC and BMD of postmenopausal BCSs. BMC was an outcome in three studies. One study favoured exercise (Irwin, Alvarez-Reeves, et al., 2009 [12 month]) and in two studies exercise had an adverse effect on the BMC of postmenopausal BCSs (Irwin, Alvarez-Reeves, et al., 2009 [6 month]; Saarto et al., 2012) (Table 15; Fig. 12).

Eight BMD outcomes were reported across four studies. Five outcomes across three studies favoured exercise (Irwin, Alvarez-Reeves, et al., 2009 [6 month]; Saarto et al., 2012; Winters-Stone et al., 2011), two outcomes from two studies favoured neither exercise or control conditions (Irwin, Alvarez-Reeves, et al., 2009 [6 month]; Saarto et al., 2012), and one outcome (greater trochanter BMD) from the Winters-Stone et al. (2011) study favoured control conditions (Table 15; Fig. 13).

Winters-Stone et al. (2011) reported that 12 months of resistance exercise resulted in a statistically significant beneficial effect on the lumbar spine BMD of

postmenopausal BCSs; with a mean increase of 0.004g/cm^2 among exercisers, and a mean reduction of -0.022g/cm^2 among controls (mean difference of 0.005gcm^2; p=<0.01) (Table 17; Fig. 12). Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported that 6 months of aerobic exercise had no effect on total BMD, with both exercisers and controls losing -0.008g/cm^2. However, 12 months of aerobic exercise resulted in a statistically significant beneficial effect; exercising postmenopausal BCSs gained 0.008g/cm^2 of total BMD, whereas controls lost -0.025g/cm^2 of total BMD (mean difference of 0.033 g/cm^2; p=0.043; Table 17; Fig. 12) (Irwin, Alvarez-Reeves, et al., 2009 [12 month]). A similar trend was observed for BMC (Irwin, Alvarez-Reeves, et al., 2009). These findings demonstrate the importance of the maintenance of weight bearing exercise throughout the recovery stage of the breast cancer experience. Postmenopausal BCSs who walk five times a week, for 30min, may need to maintain this exercise regime for longer than 6 months, in order to achieve improvements in total BMC and BMD.

It has been reported that a 1 to 2% increase in BMD translates to a 7 to 14% decrease in fracture risk (Wasnich & Miller, 2000). Irwin, Alvarez-Reeves, et al. (2009) [12 month] reported a mean percentage increase in total BMD of 0.2% among exercisers, and a mean percentage reduction of 1.7% among controls. Similarly Winters-Stone et al. (2011) reported a mean percentage increase in lumbar spine BMD of 0.41% among exercisers, and a mean percentage reduction of -1.27% among controls. Although these exercising postmenopausal BCSs did not increase their BMD in a clinically significant way, they were able to maintain BMD, whereas controls experienced clinically significant reductions in BMD. It could be speculated that exercising

postmenopausal BCSs had a 7 to 14% reduced risk of fracture compared to non-exercising postmenopausal BCSs. However longitudinal studies with long term follow-up are required to determine if this is the case.

No statistically significant effects of exercise were reported by Saarto et al. (2012) at the lumbar spine or femoral neck, or by Winters-Stone et al. (2011) at the total hip, greater trochanter or femoral neck (Table 15; Fig. 13). The mixed findings between studies may be due to different responses to exercise at the different BMD measurement sites. However it is possible that age acted as a significant confounder, as Winters-Stone, Leo, and Schwartz (2012) recently reported that age moderated the effect of exercise on BMD; with younger postmenopausal BCSs more likely to experience a positive net effect of exercise than older postmenopausal BCSs.

The limited evidence available from this review suggests that exercise has the potential to prevent the losses in BMD, which may otherwise occur, in postmenopausal BCSs. However it is advisable that exercising postmenopausal BCSs have their BMD monitored at regular intervals.

5.8. Moderating effect of bisphosphonates on the BMD of postmenopausal BCSs

Bisphosphonates are often prescribed to increase BMD in postmenopausal BCSs; however they can have unpleasant side effects such as gastrointestinal disturbance (Irwin, Alvarez-Reeves, et al., 2009). Waltman et al. (2010) reported that bisphosphonates resulted in increases in BMD at the total hip (1.8%; p=<0.0001), lumbar spine (2.85%; p=<0.0001) and femoral neck (0.63%; p=0.14) in postmenopausal BCSs with bone loss. Additional increases of

0.34% at the total hip, 0.23% at the lumbar spine and 0.29% at the femoral neck were reported among exercising postmenopausal BCSs who took bisphosphonates. Therefore, it is possible that the use of bisphosphonates may be a confounding factor in exercise and BMD research among postmenopausal BCSs. Future studies should seek to control for bisphosphonate use.

Irwin, Alvarez-Reeves, et al. (2009) reported that 12 months of aerobic exercise resulted in statistically and clinically significant increases in total BMD; even among a postmenopausal BCS population with low levels of bisphosphonate use (13% of the exercise group and 3% of the control group). In this study, exercising postmenopausal BCSs were able to maintain BMD whilst reducing BM and FM (Irwin, Alvarez-Reeves, et al., 2009 [12 month]). This is significant, because the major source of oestrogens in postmenopausal women is from the aromatisation of androgens in adipose tissue (Key, Allen, et al., 2001). Reductions in FM may result in a greater reduction in oestrogens and, given the positive effect of oestrogen on BMD, a greater reduction in BMD. However in the study of Irwin, Alvarez-Reeves, et al. (2009) [12 month] aerobic exercise, in the form of walking, was able to negate this effect and BMD was maintained even though BM and FM were lost. If these results were replicated in larger studies, it is possible that walking may prove to be an effective alternative to bisphosphonate use, and postmenopausal BCSs may be able to maintain BMD, and reduce their fracture risk, without the unpleasant side effects associated with bisphosphonates.

5.9. Moderating effect of AI use on the body composition of postmenopausal BCSs

AIs are commonly prescribed as part of the treatment regime for oestrogen receptor positive postmenopausal breast cancers (Appendix 4). However, AIs can reduce oestrogen to undetectable levels, and AIs have been associated with greater reductions in BMD, and an increased risk of fracture compared to AOs (Rizzoli et al., 2012). Saarto et al. (2012) reported that among postmenopausal BCSs, mean bone losses at the femoral neck were; -1.8%, -0.4% and -0.2% for those on AIs, AOs and no hormone therapy respectively. van Londen et al. (2011) recently reported that statistically significant greater increases in LBM were observed among AI users than non AI users; whereas FM increased significantly among non AI users and remained stable among AI users. It was speculated that these differences may be due to the significantly higher free testosterone levels, and significantly lower SHBG levels, that were observed among BCSs who were AI users (van Londen et al., 2011).

However Winters-Stone et al. (2011) reported that neither AI use, nor AO use had any moderating effect on FM or any measure of BMD among postmenopausal BCSs. In contrast, Irwin, Alvarez-Reeves, et al. (2009) [6 month] reported that exercising postmenopausal BCSs who were taking AIs (n=10) maintained their BMD and BMC; whereas control postmenopausal BCSs who were taking AIs (n=15) experienced reductions in BMD and BMC. In addition, reductions in FM and increases in LBM were seen among exercising AI users, whereas FM was maintained and LBM was reduced among control AI users (Irwin, Alvarez-Reeves, et al., 2009 [6 month]). These findings suggest that exercise can attenuate AI related bone loss, and result in additional

beneficial body composition changes among postmenopausal BCSs who are prescribed AIs. However, caution must be taken when interpreting these findings, as statistical power may have been compromised, due to the small number of participants included in this stratified analysis (Irwin, Alvarez-Reeves, et al., 2009).

Although it is possible that exercise can overcome the detrimental effect of AIs on BMD, it is not possible to draw conclusions from the limited studies available. From the limited evidence, it is not possible to determine if AI use has a beneficial effect on the LBM and/or FM of postmenopausal BCS. It is also not known if exercise has a synergistic effect, and functions with AIs, to induce greater beneficial effects on LBM and/or FM. This is an area which requires further study, and future studies should include sufficient sample sizes to enable body composition outcomes to be stratified by type of hormone therapy use, without statistical power being compromised.

5.10. Additional benefits of exercise: improvements in quality of life, survival and prognostic biomarkers among postmenopausal BCSs

Aside from the effect of exercise on body composition; exercise may have additional health benefits for postmenopausal BSCs. A recent review has confirmed that exercise can improve health related quality of life in BCSs (Mishra et al., 2012). Another recent review has reported that there is fairly consistent evidence of an inverse association between post-diagnosis PA, and risk of breast-cancer-specific and all-cause mortality (Ballard-Barbash et al., 2012). This association was not modified by menopausal status; suggesting that both premenopausal and postmenopausal BCSs can benefit from post-

diagnosis exercise (Ballard-Barbash et al., 2012). However, only one study has investigated the effect of exercise on survival among an exclusively postmenopausal sample of BCSs (Irwin et al., 2011). In this longitudinal study, postmenopausal BCSs who undertook >150min a week of moderate intensity recreational PA, after diagnosis had lower breast-cancer-specific mortality (HR = 0.61; [95%CI 0.35-0.99]; p=0.049) and lower all-cause mortality (HR = 0.54; [95%CI 0.38-0.79]; p=<0.01). The effect on all-cause mortality was observed even among those who were inactive prior to diagnosis; and BMI did not have any moderating effect on survival (Irwin et al., 2011).

A number of different mechanisms have been proposed to explain the relationship between PA and survival following breast cancer (Courneya et al., 2004). It is possible that PA and exercise exert a beneficial effect, via the reduction of circulating oestrogens. Exercise has been shown to reduce circulating oestrogens in healthy postmenopausal women (Friedenreich et al., 2010; McTiernan et al., 2004). And some studies have demonstrated a stronger inverse relationship between PA and mortality in BCSs with oestrogen positive receptive tumours (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Irwin et al., 2011; Irwin et al., 2008).

Exercise may also exert its beneficial effect on survival among postmenopausal BCSs via reductions in important prognostic biomarkers, related to the insulin and inflammatory pathways. Irwin, McTiernan, Bernstein, et al. (2005) reported higher PA was associated with beneficial effects on the insulin pathway in both premenopausal and postmenopausal women. And Irwin, McTiernan, Bernstein, et al. (2005) and Pierce et al. (2009) reported that higher levels of PA were statistically significantly associated with lower circulating levels of C-reactive

protein (CRP) (a marker of inflammation); and that higher CRP levels were associated with higher BMI and greater WC. In addition several RCTs among postmenopausal BCSs have demonstrated that exercise has beneficial effects on; the insulin pathway (Fairey et al., 2003; Irwin, Varma, et al., 2009), inflammation (Fairey, Courneya, Field, Bell, Jones, Martin, et al., 2005) and immune function (Fairey, Courneya, Field, Bell, Jones, & Mackey, 2005).

Evidence from the limited number of studies available, suggests that higher levels of post-diagnosis exercise are associated with improvements in prognostic biomarkers and survival among postmenopausal BCSs. In addition higher BMI and WC have been negatively associated with prognostic biomarkers. However, studies investigating the effects of exercise related changes in BM or body composition on prognostic biomarkers and survival among postmenopausal BCSs have not been conducted. Therefore, it is not possible to determine if post-diagnosis exercise exerts its positive effects via a direct effect, indirectly via body composition changes, or via a combination of the two. This is an area which warrants further study.

5.11. Limitations: risk of bias associated with individual studies

The Downs and Black Checklist (1998) reporting subtotal percentage scores of individual studies ranged from 73% to 100% (Table 16). Therefore, it was likely that the reporting of studies was of sufficient quality to enable the conduct, reliability and validity of studies to be adequately assessed.

The total methodological quality of individual studies was generally high; with total Downs and Black Checklist (1998) methodological quality percentage scores of 72%; 78%, 88% 88% and 91% (Table 16). The overall risk of bias

associated with individual studies was low, and therefore the findings were likely to be true. However external validity subtotal percentage scores ranged from 33% to 67% and none of the included studies scored on question 12 of the Downs and Black Checklist (1998) (Table 16; Appendices 15 & 16). Question 12 related to the representativeness of the sample; therefore it is possible that the results of individual studies, and therefore this review, may not reflect the entire postmenopausal BCS population and this raises questions about the generalisation of results. Internal validity (bias) subtotal percentage scores ranged from 71% to 86% (Table 16). Overall these scores suggest that the results were not systematically different from the true effect. However, none of the included studies scored on question 14 of the Downs and Black Checklist (1998) (Appendices 15 & 16). Although this was expected due to the inherent difficulties of participant blinding in exercise intervention studies, and although unavoidable, the lack of participant blinding may have led to an overestimate of the treatment effect.

5.12. Limitations: risk of bias at the review level

A comprehensive search strategy was conducted, so as to minimise publication bias. However comprehensive searching may not have been sufficient to prevent bias, as detecting and correcting potential biases is problematic (Sterne et al., 2011). For example Song et al. (2009) reported that publication bias occurred early in the research process, before the presentation of findings at conferences or submission of manuscripts to journals. Although the exclusion of abstract only publications from this review was necessary for practical reasons (see p.42), it is possible that studies with non-significant findings may

have been published as abstracts, but may not have reached full publication. Therefore the potential for publication bias, and the associated overestimate of intervention effects, cannot be excluded from this review.

The risk of citation bias in this review is minimal, as the reference lists of potentially relevant studies were not searched to locate other relevant records.

Attempts were made to identify duplicate publications (see p.43), however it may be difficult or impossible to identify duplicate publications, as they may not cross reference each other or share common authors, and they may have different numbers of participants and report different outcomes (Centre for Reviews and Dissemination, 2009, p. 25; Higgins & Deeks, 2011; von Elm, Poglia, Walder, & Tramer, 2004). Substantial biases can be introduced into a review if studies are included more than once (Tramer, Reynolds, Moore, & McQuay, 1997). Therefore the potential for duplicate publication bias cannot be excluded from this review.

To minimise the effect of time-lag bias, the search for records was updated once during the review process, and studies published up until the End of June 2012 were included. However, all of the studies included in this review were published within the last decade, indicating that exercise and cancer survivorship research is a relatively new and rapidly expanding research area. Therefore the risk of time lag bias cannot be excluded from this review.

Although the search strategy included non-English language records; due to the practical and financial issues involved in translation, non-English language studies were excluded from the final review (see p.40-42). The imposition of English language restrictions may have introduced language bias, and this is a limitation of this review.

As body composition outcomes have frequently been secondary outcomes in exercise and BCS research, it was not possible to determine if insignificant or null body composition findings were subject to selective non-reporting. Therefore the potential for outcome reporting bias is a limitation of this review.

Decisions about which studies should be included in a systematic review, and which data should be extracted from them, require judgment and are therefore subjective (Centre for Reviews and Dissemination, 2009; Higgins & Deeks, 2011).

Compared to two reviewers, the use of a single reviewer has been associated with a greater number of errors, in relation to the screening of records, and the extraction of data (Buscemi, Hartling, Vandermeer, Tjosvold, & Klassen, 2006; Edwards et al., 2002). Therefore, in order to increase objectivity and minimise bias it has been recommended that, whenever possible, the systematic review process should be conducted by at least two reviewers (Centre for Reviews and Dissemination, 2009; Higgins & Deeks, 2011).

Only one reviewer was available to perform the review process for this MSc dissertation. Although this single reviewer did not receive any rewards from, and was not affiliated to any organisations which may have had a vested interested in the review outcomes, the use of a single reviewer may have introduced subjectivity, selection bias and a greater number of errors. Therefore single reviewer bias is a limitation of this systematic review.

6.0. Conclusion

This systematic review found that a wide variety of aerobic and resistance exercises could be performed safely by postmenopausal BCSs. Although the findings were mixed; exercise appeared to have a small favourable effect on the BM, BMI, WC, LBM, FM, BF%, BMC and BMD of postmenopausal BCSs. Exercise had a greater beneficial effect on body composition than on BM or BMI. Statistically significant beneficial effects of exercise were reported for BM and BMI, LBM, BF%, total BMD and lumbar spine BMD in at least one included study. However, whether these statistically significant benefits result in a clinically significant effect remains to be seen.

The greatest beneficial effects of exercise on the BM, BMI and WC of postmenopausal BCSs were reported by Rahnama et al. (2010), and the greatest beneficial effects of exercise on the LBM, FM and BF% of postmenopausal BCSs were reported by Herrero et al. (2006). The studies of Rahnama et al. (2010) and Herrero et al. (2006) were the only two included studies to prescribe a combination of aerobic and resistance exercise, and both studies had exercise interventions with short total durations. It is possible greater benefits could be achieved if a combination of aerobic and resistance exercises were maintained over longer total exercise durations; and further studies of this type of exercise are warranted.

A beneficial effect of aerobic exercise was also noted, and walking five times a week, for 30min, for 12 months, resulted in reductions in BM and FM, increases in LBM, and the maintenance of BMD, even among postmenopausal BCSs who were at high risk of bone loss (Irwin, Alvarez-Reeves, et al., 2009 [12 month]).

The major limitation of this systematic review was the lack of generalisation of the findings, due to the relatively low total number of included participants. In addition, the risk of single reviewer bias and publication biases remain. There was also the risk that included exercise interventions did not provide an adequate training stimulus, due to poor exercise adherence. Further research is required to develop strategies to improve exercise adherence among postmenopausal BCSs.

To the author's best knowledge this is the first systematic review to determine the effects of exercise on body composition in an exclusively postmenopausal BCS population; and this was a major strength of this review. Other strengths of this systematic review were; the extensive search strategy which sought to minimise bias, the use of a HQTS tool to ensure that exercise provided an adequate training stimulus, the high methodological quality and the low risk of bias of included studies, and the inclusion of studies which used valid and reliable methods of body composition analysis (e.g. DEXA and combined BMI and WC).

At present the evidence from this review is not sufficient to enable specific exercise prescriptions, designed to induce beneficial body composition changes in postmenopausal BCSs, to be made. Further research with larger sample sizes, to allow for stratification of results by important confounding factors, would enable the effects of specific exercise prescriptions on the BM and body composition of postmenopausal BCSs to be elucidated. This would be of benefit to health and fitness professionals and to individual postmenopausal BCSs.

References

Adept Scientific. (2011). EndNote (Version X5.0.1) [computer program]. Letchworth, UK: Adept Scientific.

Alberti, K. G., Zimmet, P., & Shaw, J. (2006). Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Medicine, 23*(5), 469-480. doi: 10.1111/j.1464-5491.2006.01858.x

American College of Sports Medicine. (2006). *ACSM's guidelines for exercise testing and prescription.* (7th ed.). Philadelphia: Lippincott Williams and Wilkins.

Armijo-Olivo, S., Macedo, L. G., Gadotti, I. C., Fuentes, J., Stanton, T., & Magee, D. J. (2008). Scales to assess the quality of randomized controlled trials: a systematic review. *Physical Therapy, 88*(2), 156-175. doi: 10.2522/ptj.20070147

Armijo-Olivo, S., Stiles, C. R., Hagen, N. A., Biondo, P. D., & Cummings, G. G. (2010). Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. *Journal of Evaluation in Clinical Practice, 18*(1), 12-18. doi: 10.1111/j.1365-2753.2010.01516.x

Ballard-Barbash, R., Friedenreich, C. M., Courneya, K. S., Siddiqi, S. M., McTiernan, A., & Alfano, C. M. (2012). Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *Journal of the National Cancer Institute, 104*(11), 815-840. doi: 10.1093/jnci/djs207

Barone, B. B., Yeh, H. C., Snyder, C. F., Peairs, K. S., Stein, K. B., Derr, R. L., . . . Brancati, F. L. (2008). Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *Journal of the American Medical Association, 300*(23), 2754-2764. doi: 10.1001/jama.2008.824

Battaglini, C., Naumann, F., Groff, D., Shields, E., Hackney, A. C., & Peppercorn, J. (2011). Comparison of body composition assessment methods in breast cancer survivors. *Oncology Nursing Forum, 38*(4), E283-290. doi: 10.1188/11.onf.e283-e290

Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., . . . Stroup, D. F. (1996). Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *Journal of the American Medical Association, 276*(8), 637-639. doi: 10.1001/jama.1996.03540080059030

Bergstrom, A., Pisani, P., Tenet, V., Wolk, A., & Adami, H. O. (2001). Overweight as an avoidable cause of cancer in Europe. *International Journal of Cancer, 91*(3), 421-430. doi: 10.1002/1097-0215(200002)

Bianchini, F., Kaaks, R., & Vainio, H. (2002). Overweight, obesity, and cancer risk. *The Lancet Oncology, 3*(9), 565-574. doi: 10.1016/S1470-2045(02)00849-5

Boyle, P., & Levin, B. (Eds.). (2008). *World Cancer Report 2008*. Lyon:France: International Agency for Research on Cancer.

Bradshaw, P. T., Ibrahim, J. G., Stevens, J., Cleveland, R., Abrahamson, P. E., Satia, J. A., . . . Gammon, M. D. (2012). Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. *Epidemiology, 23*(2), 320-327. doi: 10.1097/EDE.0b013e31824596a1

Bray, F., McCarron, P., & Parkin, D. M. (2004). The changing global patterns of female breast cancer incidence and mortality. *Breast Cancer Research, 6*(6), 229-239. doi: 10.1186/bcr932

Breakthrough Breast Cancer. (2009). The Best Treatment: Your guide to breast cancer treatment in England and Wales (2nd ed.). Retrieved February 04, 2012, from http://www.breakthrough.org.uk/breast_cancer/treatment/index.html?gclid=CIH11fnJwKwCFUtC4Qodhh5PrA

British Nutrition Foundation. (1999). *Obesity: The report of the British Nutrition Foundation Task Force*. Oxford: Blackwell Science.

Brouwers, M. C., Johnston, M. E., Charette, M. L., Hanna, S. E., Jadad, A. R., & Browman, G. P. (2005). Evaluating the role of quality assessment of

primary studies in systematic reviews of cancer practice guidelines. *BMC Medical Research Methodology, 5*(1), 8. doi: 10.1186/1471-2288-5-8

Brown, B. W., Brauner, C., & Minnotte, M. C. (1993). Noncancer deaths in white adult cancer patients. *Journal of the National Cancer Institute, 85*(12), 979-987. doi: 10.1093/jnci/85.12.979

Brown, J. K., Byers, T., Doyle, C., Coumeya, K. S., Demark-Wahnefried, W., Kushi, L. H., . . . American Cancer, S. (2003). Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA: A Cancer Journal for Clinicians, 53*(5), 268-291. doi: 10.3322/canjclin.53.5.268

Buscemi, N., Hartling, L., Vandermeer, B., Tjosvold, L., & Klassen, T. P. (2006). Single data extraction generated more errors than double data extraction in systematic reviews. *Journal of Clinical Epidemiology, 59*(7), 697-703. doi: 10.1016/j.jclinepi.2005.11.010

Caan, B. J., Emond, J. A., Natarajan, L., Castillo, A., Gunderson, E. P., Habel, L., . . . Pierce, J. P. (2006). Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. *Breast Cancer Research and Treatment, 99*(1), 47-57. doi: 10.1007/s10549-006-9179-y

Caan, B. J., Flatt, S. W., Rock, C. L., Ritenbaugh, C., Newman, V., & Pierce, J. P. (2000). Low-energy reporting in women at risk for breast cancer recurrence. Women's Healthy Eating and Living Group. *Cancer*

Epidemiology, Biomarkers & Prevention, 9(10), 1091-1097. Retrieved from http://cebp.aacrjournals.org/content/9/10/1091.long

Caan, B. J., Kwan, M. L., Hartzell, G., Castillo, A., Slattery, M. L., Sternfeld, B., & Weltzien, E. (2008). Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. *Cancer Causes Control, 19*(10), 10. doi: 10.1007/s10552-008-9203-0

Camoriano, J. K., Loprinzi, C. L., Ingle, J. N., Therneau, T. M., Krook, J. E., & Veeder, M. H. (1990). Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. *Journal of Clinical Oncology, 8*(8), 1327-1334.

Campbell, A., Stevinson, C., & Crank, H. (2011). The BASES Expert Statement on Exercise and Cancer Survivorship. *The Sport and Exercise Scientist, Summer 2011*(28), 16-17. Retrieved from http://www.bases.org.uk/Exercise-and-Cancer

Campbell, K. L., Neil, S. E., & Winters-Stone, K. M. (2011). Review of exercise studies in breast cancer survivors: attention to principles of exercise training. *British Journal of Sports Medicine*. doi: 10.1136/bjsm.2010.082719

Cancer Research UK. (2009). Breast cancer - survival statistics. Retrieved March 28, 2012, from http://info.cancerresearchuk.org/cancerstats/types/breast/survival

Cancer Research UK. (2011a). Breast cancer - UK incidence statistics. Retrieved March 28, 2012, from http://info.cancerresearchuk.org/cancerstats/types/breast/incidence

Cancer Research UK. (2011b, January 14, 2011). Number stages of breast cancer. Retrieved February 20, 2012, from http://cancerhelp.cancerresearchuk.org/type/breast-cancer/treatment/number-stages-of-breast-cancer

Cancer Research UK. (2011c, January 14, 2011). TNM breast cancer staging. Retrieved February 20, 2012, from http://cancerhelp.cancerresearchuk.org/type/breast-cancer/treatment/tnm-breast-cancer-staging

Cancer Research UK. (2011d, January 11, 2011). Types of breast cancer. Retrieved February 20, 2012, from http://cancerhelp.cancerresearchuk.org/type/breast-cancer/about/types/

Cancer Research UK. (2012). Breast cancer - risk factors. Retrieved March 28, 2012, from http://info.cancerresearchuk.org/cancerstats/types/breast/riskfactors

Carter, A. O., Griffin, G. H., & Carter, T. P. (2006). A survey identified publication bias in the secondary literature. [Review]. *Journal of Clinical Epidemiology, 59*(3), 241-245. doi: 10.1016/j.jclinepi.2005.08.011

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports, 100*(2), 126-131. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1424733/

Centre for Reviews and Dissemination. (2009). *Systematic Reviews: CRD's guidance for Undertaking Reviews in Health Care*. York: Centre for Reviews and Dissemination, University of York.

Chan, A. W., & Altman, D. G. (2005). Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *British Medical Journal, 330*(7494), 753. doi: 10.1136/bmj.38356.424606.8F

Chan, A. W., Hrobjartsson, A., Haahr, M. T., Gotzsche, P. C., & Altman, D. G. (2004). Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *Journal of the American Medical Association, 291*(20), 2457-2465. doi: 10.1001/jama.291.20.2457

Cheema, B., & Gaul, C. A. (2006). Full-body exercise training improves fitness and quality of life in survivors of breast cancer. *Journal of Strength and Conditioning Research, 20*(1), 14.

Cheema, B., Gaul, C. A., Lane, K., & Fiatarone Singh, M. A. (2008). Progressive resistance training in breast cancer: a systematic review of

clinical trials. *Breast Cancer Research and Treatment, 109*(1), 9-26. doi: 10.1007/s10549-007-9638-0

Chen, Z., Maricic, M., Aragaki, A. K., Mouton, C., Arendell, L., Lopez, A. M., . . . Chlebowski, R. T. (2009). Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: results from the Women's Health Initiative. *Osteoporosis International, 20*(4), 527-536. doi: 10.1007/s00198-008-0721-0

Cheney, C. L., Mahloch, J., & Freeny, P. (1997). Computerized tomography assessment of women with weight changes associated with adjuvant treatment for breast cancer. *The American Journal of Clinical Nutrition, 66*(1), 141-146. Retrieved from http://www.ajcn.org/content/66/1/141.full.pdf+html

Chien, A. J., & Goss, P. E. (2006). Aromatase inhibitors and bone health in women with breast cancer. *Journal of Clinical Oncology, 24*(33), 5305-5312. doi: 10.1200/JCO.2006.07.5382

Chlebowski, R. T., Aiello, E., & McTiernan, A. (2002). Weight loss in breast cancer patient management. *Journal of Clinical Oncology, 20*(4), 1128-1143.

Cornier, M. A., Despres, J. P., Davis, N., Grossniklaus, D. A., Klein, S., Lamarche, B., . . . Stroke, C. (2011). Assessing adiposity: a scientific statement from the american heart association. *Circulation, 124*(18), 1996-2019. doi: 10.1161/CIR.0b013e318233bc6a

Courneya, K. S., & Friedenreich, C. M. (2007). Physical activity and cancer control. *Seminars in Oncology Nursing, 23*(4), 242-252. doi: 10.1016/j.soncn.2007.08.002

Courneya, K. S., Jones, L. W., Fairey, A. S., Campbell, C., Ladha, A. B., Friedenreich, C. M., & Mackey, J. R. (2004). Physical activity in cancer survivors: implications for recurrence and mortality. *Cancer Therapy, 2*, 1-12.

Courneya, K. S., Mackey, J. R., Bell, G. J., Jones, L. W., Field, C. J., & Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *Journal of Clinical Oncology, 21*(9), 1660-1668. doi: 10.1200/jco.2003.04.093

Crank, H., & Daley, A. (2010). Exercise after treatment for breast cancer: Effects on quality of life. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 53-72). New York: Springer.

Crombie, I. K. (1996). *The Pocket Guide to Critical Appraisal*. London: BMJ Publishing Group.

Decullier, E., Lheritier, V., & Chapuis, F. (2005). Fate of biomedical research protocols and publication bias in France: retrospective cohort study. *British Medical Journal, 331*(7507), 19. doi: 10.1136/bmj.38488.385995.8F

Deeks, J. J., Dinnes, J., D'Amico, R., Sowden, A. J., Sakarovitch, C., Song, F., . . . Group, E. C. S. T. C. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment, 7*(27), 1-173.

Del Rio, G., Zironi, S., Valeriani, L., Menozzi, R., Bondi, M., Bertolini, M., . . . Federico, M. (2002). Weight gain in women with breast cancer treated with adjuvant cyclophosphomide, methotrexate and 5-fluorouracil. Analysis of resting energy expenditure and body composition. *Breast Cancer Research and Treatment, 73*(3), 267-273. doi: 10.1023/A:1015892714162

Demark-Wahnefried, W., Hars, V., Conaway, M. R., Havlin, K., Rimer, B. K., McElveen, G., & Winer, E. P. (1997). Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. *The American Journal of Clinical Nutrition, 65*(5), 1495-1501. Retrieved from http://www.ajcn.org/content/65/5/1495.long

Demark-Wahnefried, W., Morey, M. C., Sloane, R., Snyder, D. C., Miller, P. E., Hartman, T. J., & Cohen, H. J. (2012). Reach out to enhance wellness home-based diet-exercise intervention promotes reproducible and sustainable long-term improvements in health behaviors, body weight, and physical functioning in older, overweight/obese cancer survivors. *Journal of Clinical Oncology, 30*(19), 2354-2361. doi: 10.1200/JCO.2011.40.0895

Demark-Wahnefried, W., Rimer, B. K., & Winer, E. P. (1997). Weight gain in women diagnosed with breast cancer. *Journal of the American Dietetic Association, 97*(5), 519-526. Retrieved from www.adajournal.org

Department of Health. (2011). *Start Active, Stay Active: A report on physical activity from the four home countries' Chief Medical Officers*. UK: Department of Health.

Dignam, J. J., Wieand, K., Johnson, K. A., Fisher, B., Xu, L., & Mamounas, E. P. (2003). Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. *Journal of the National Cancer Institute, 95*(19), 1467-1476. doi: 10.1093/jnci/djg060

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health, 52*(6), 377-384. doi: 10.1136/jech.52.6.377

Doyle, C., Kushi, L. H., Byers, T., Courneya, K. S., Demark-Wahnefried, W., Grant, B., . . . American Cancer, S. (2006). Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA: A Cancer Journal for Clinicians, 56*(6), 323-353. doi: 10.3322/canjclin.56.6.323

Dwan, K., Altman, D. G., Arnaiz, J. A., Bloom, J., Chan, A. W., Cronin, E., . . . Williamson, P. R. (2008). Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLoS One, 3*(8), e3081. doi: 10.1371/journal.pone.0003081

Easterbrook, P. J., Berlin, J. A., Gopalan, R., & Matthews, D. R. (1991). Publication bias in clinical research. *Lancet, 337*(8746), 867-872. doi: 10.1016/0140-6736(91)90201-Y

Edwards, P., Clarke, M., DiGuiseppi, C., Pratap, S., Roberts, I., & Wentz, R. (2002). Identification of randomized controlled trials in systematic reviews: accuracy and reliability of screening records. *Statistics in Medicine, 21*(11), 1635-1640. doi: 10.1002/sim.1190

Effective Public Health Practice Project. (2003, June 2 2009). Quality assessment tool for quantitative studies Retrieved April 1, 2012, from http://www.hamilton.ca/healthandsocialservices/research/ephpp/ephpp.htm

Egger, M., Juni, P., Bartlett, C., Holenstein, F., & Sterne, J. (2003). How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technology Assessment, 7*(1), 1-76. Retrieved from http://www.hta.ac.uk/execsumm/summ701.htm

Egger, M., & Smith, G. D. (1998). Meta-analysis bias in location and selection of studies. *British Medical Journal, 316*(7124), 61-66. doi: 10.1136/bmj.316.7124.61

Egger, M., Zellweger-Zahner, T., Schneider, M., Junker, C., Lengeler, C., & Antes, G. (1997). Language bias in randomised controlled trials published

in English and German. *Lancet, 350*(9074), 326-329. doi: 10.1016/S0140-6736(97)02419-7

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., & Mackey, J. R. (2003). Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. *Cancer Epidemiology, Biomarkers & Prevention, 12*(8), 721-727. Retrieved from http://cebp.aacrjournals.org

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., & Mackey, J. R. (2005). Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *Journal of Applied Physiology, 98*(4), 1534-1540. doi: 10.1152/japplphysiol.00566.2004

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., Martin, B. S., & Mackey, J. R. (2005). Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. *Brain, Behavior, and Immunity, 19*(5), 381-388. doi: 10.1016/j.bbi.2005.04.001

Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer, 127*(12), 2893-2917. doi: 10.1002/ijc.25516

Fong, D. Y. T., Ho, J. W. C., Hui, B. P. H., Lee, A. M., Macfarlane, D. J., Leung, S. S. K., . . . Cheng, K. k. (2012). Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *British Medical Journal, 344*, e70. doi: 10.1136/bmj.e70

Forbes, G. B., Brown, M. R., Welle, S. L., & Lipinski, B. A. (1986). Deliberate overfeeding in women and men: energy cost and composition of the weight gain. *British Journal of Nutrition, 56*(1), 1-9. doi: 10.1079/BJN19860080

Freedman, R. J., Aziz, N., Albanes, D., Hartman, T., Danforth, D., Hill, S., . . . Yanovski, J. A. (2004). Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. *The Journal of Clinical Endocrinology & Metabolism, 89*(5), 2248-2253. doi: 10.1210/jc.2003-031874

Friedenreich, C. M., Woolcott, C. G., McTiernan, A., Ballard-Barbash, R., Brant, R. F., Stanczyk, F. Z., . . . Courneya, K. S. (2010). Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. *Journal of Clinical Oncology, 28*(9), 1458-1466. doi: 10.1200/jco.2009.24.9557

Genton, L., Kyle, U. G., Balmer Majno, S., & Pichard, C. (2006). Body composition changes in breast cancer patients during curative radiation therapy. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 1*(1), 2-8. doi: 10.1016/j.eclnm.2006.07.005

Goodwin, P. J., Ennis, M., Pritchard, K. I., McCready, D., Koo, J., Sidlofsky, S., . . . Redwood, S. (1999). Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *Journal of Clinical Oncology, 17*(1), 120-129. Retrieved from http://jco.ascopubs.org/content/17/1/120.full.pdf+html

Gotzsche, P. C. (1987). Reference bias in reports of drug trials. *British Medical Journal (Clinical Research Edition), 295*(6599), 654-656.

Gotzsche, P. C. (1989). Multiple publication of reports of drug trials. *European Journal of Clinical Pharmacology, 36*(5), 429-432.

Green, S., & Higgins, J. P. T. (2011). Chapter 2: Preparing a Cochrane review. In S. Green & J. P. T. Higgins (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org.

Green, S., Higgins, J. P. T., Alderson, P., Clarke, M., Mulrow, C. D., & Oxman, A. D. (2011). Chapter 1: Introduction. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org

Guo, S. S., Zeller, C., Chumlea, W. C., & Siervogel, R. M. (1999). Aging, body composition, and lifestyle: the Fels Longitudinal Study. *American Journal*

of Clinical Nutrition, 70(3), 405-411. Retrieved from http://www.ajcn.org/content/70/3/405.full.pdf+html

Han, A., Robinson, V., Judd, M., Taixiang, W., Wells, G., & Tugwell, P. (2004). Tai chi for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews*(3), CD004849. doi: 10.1002/14651858.CD004849

Hartling, L., Ospina, M., Liang, Y., Dryden, D. M., Hooton, N., Krebs Seida, J., & Klassen, T. P. (2009). Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *British Medical Journal, 339*, b4012. doi: 10.1136/bmj.b4012

Harvie, M. (2010). The importance of controlling body weight after a diagnosis of breast cancer: The role of diet and exercise in breast cancer patient management. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 73-96). New York: Springer.

Harvie, M., Campbell, I. T., Baildam, A., & Howell, A. (2004). Energy balance in early breast cancer patients receiving adjuvant chemotherapy. *Breast Cancer Research and Treatment, 83*(3), 201-210. doi: 10.1023/B:BREA.0000014037.48744.fa

Harvie, M., & Howell, A. (2006). Incorporating weight control into management of patients with early breast cancer in the UK. In A. McTiernan (Ed.), *Cancer Prevention and Management through Exercise and Weight Control* (pp. 535-560). Boca Raton; FL: CRC Press.

Harvie, M., Howell, A., Thatcher, N., Baildam, A., & Campbell, I. (2005). Energy balance in patients with advanced NSCLC, metastatic melanoma and metastatic breast cancer receiving chemotherapy--a longitudinal study. *British Journal of Cancer, 92*(4), 673-680. doi: 10.1038/sj.bjc.6602357

Hayes, S. C., Spence, R. R., Galvão, D. A., & Newton, R. U. (2009). Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. *Journal of Science & Medicine in Sport, 12*(4), 428-434. doi: 10.1016/j.jsams.2009.03.002

Heber, D., Ingles, S., Ashley, J. M., Maxwell, M. H., Lyons, R. F., & Elashoff, R. M. (1996). Clinical detection of sarcopenic obesity by bioelectrical impedance analysis. *The American Journal of Clinical Nutrition, 64*(3S), 472S-477S. Retrieved from http://ajcn.nutrition.org

Heideman, W. H., Russell, N. S., Gundy, C., Rookus, M. A., & Voskuil, D. W. (2009). The frequency, magnitude and timing of post-diagnosis body weight gain in Dutch breast cancer survivors. *European Journal of Cancer, 45*(1), 119-126. doi: 10.1016/j.ejca.2008.09.003

Herrero, F., San Juan, A. F., Fleck, S. J., Balmer, J., Perez, M., Canete, S., . . . Lucia, A. (2006). Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial. *International Journal of Sports Medicine, 27*(7), 573-580.

Heyward, V. H., & Wagner, D. R. (2004). *Applied body composition assessment* (2nd ed.). Champaign, IL: Human Kinetics.

Higgins, J. P. T., Altman, D. G., & Sterne, J. A. C. (2011). Chapter 8: Assessing risk of bias in included studies. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org.

Higgins, J. P. T., & Deeks, J. J. (2011). Chapter 7: Selecting studies and collecting data. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from http://www.cochrane-handbook.org.

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *Journal of the American Medical Association, 293*(20), 2479-2486. Retrieved from http://jama.jamanetwork.com

Hopewell, S., Clarke, M., Lefebvre, C., & Scherer, R. (2007). Handsearching versus electronic searching to identify reports of randomized trials. *Cochrane Database of Systematic Reviews 2007*(2), MR000001. doi: 10.1002/14651858.MR000001.pub2

Hopewell, S., Clarke, M., Stewart, L., & Tierney, J. (2007). Time to publication for results of clinical trials (Review). [Review]. *Cochrane Database of Systematic Reviews 2007*(2), MR000011. doi: 10.1002/14651858.MR000011.pub2

Hopewell, S., Dutton, S., Yu, L. M., Chan, A. W., & Altman, D. G. (2010). The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *British Medical Journal, 340*, c723. doi: 10.1136/bmj.c723

Hopewell, S., Loudon, K., Clarke, M. J., Oxman, A. D., & Dickersin, K. (2009). Publication bias in clinical trials due to statistical significance or direction of trial results (Review). *Cochrane Database of Systematic Reviews 2009*(1). doi: 10.1002/14651858.MR000006.pub3

Hopewell, S., McDonald, S., Clarke, M., & Egger, M. (2007). Grey literature in meta-analyses of randomized trials of health care interventions. [Review]. *Cochrane Database of Systematic Reviews 2007*(2), MR000010. doi: 10.1002/14651858.MR000010.pub3

Huy, C., Schmidt, M. E., Vrieling, A., Chang-Claude, J., & Steindorf, K. (2012). Physical activity in a German breast cancer patient cohort: one-year trends and characteristics associated with change in activity level. *European Journal of Cancer, 48*(3), 297-304. doi: 10.1016/j.ejca.2011.08.005

Ingram, C., Courneya, K. S., & Kingston, D. (2006). The effects of exercise on body weight and composition in breast cancer survivors: an integrative systematic review. *Oncology Nursing Forum, 33*(5), 937-950. doi: 10.1188/06.ONF.937-950

Ioannidis, J. P. (1998). Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *Journal of the American Medical Association, 279*(4), 281-286. doi: 10.1001/jama.279.4.281

Irwin, M. L. (2010). The biological mechanisms by which physical activity might have a impact on outcome/prognosis after a breast cancer diagnosis. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 97-112). New York: Springer.

Irwin, M. L. (Ed.). (2012). *ACSM's Guide to Exercise and Cancer Survivorship*. Champaign; IL: Human Kinetics.

Irwin, M. L., Alvarez-Reeves, M., Cadmus, L., Mierzejewski, E., Mayne, S. T., Yu, H., . . . DiPietro, L. (2009). Exercise improves body fat, lean mass, and bone mass in breast cancer survivors. *Obesity (Silver Spring), 17*(8), 1534-1541. doi: 10.1038/oby.2009.18

Irwin, M. L., Crumley, D., McTiernan, A., Bernstein, L., Baumgartner, R., Gilliland, F. D., . . . Ballard-Barbash, R. (2003). Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. *Cancer, 97*(7), 1746-1757. doi: 10.1002/cncr.11227

Irwin, M. L., McTiernan, A., Baumgartner, R. N., Baumgartner, K. B., Bernstein, L., Gilliland, F. D., & Ballard-Barbash, R. (2005). Changes in body fat and weight after a breast cancer diagnosis: influence of demographic,

prognostic, and lifestyle factors. *Journal of Clinical Oncology, 23*(4), 774-782. doi: 10.1200/JCO.2005.04.036

Irwin, M. L., McTiernan, A., Bernstein, L., Gilliland, F. D., Baumgartner, R., Baumgartner, K., & Ballard-Barbash, R. (2005). Relationship of obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors. *Cancer Epidemiology, Biomarkers & Prevention 14*(12), 2881-2888. doi: 10.1158/1055-9965.EPI-05-0185

Irwin, M. L., McTiernan, A., Manson, J. E., Thomson, C. A., Sternfeld, B., Stefanick, M. L., . . . Chlebowski, R. (2011). Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. *Cancer Prevention Research, 4*(4), 522-529. doi: 10.1158/1940-6207.capr-10-0295

Irwin, M. L., Smith, A. W., McTiernan, A., Ballard-Barbash, R., Cronin, K., Gilliland, F. D., . . . Bernstein, L. (2008). Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *Journal of Clinical Oncology, 26*(24), 3958-3964. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18711185 doi:10.1200/JCO.2007.15.9822

Irwin, M. L., Varma, K., Alvarez-Reeves, M., Cadmus, L., Wiley, A., Chung, G. G., . . . Yu, H. (2009). Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale

Exercise and Survivorship study. *Cancer Epidemiology, Biomarkers & Prevention 18*(1), 306-313. doi: 10.1158/1055-9965.EPI-08-0531

Jackson, A. S., & Pollock, M. L. (1985). Practical assessment of body composition. *The Physician and Sportsmedicine, 13*(5), 79-90.

Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., & McQuay, H. J. (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? . *Controlled Clinical Trials, 17*(1), 1-12. doi: 10.1016/0197-2456(95)00134-4

Juni, P., Altman, D. G., & Egger, M. (2001). Systematic reviews in health care: Assessing the quality of controlled clinical trials. *British Medical Journal, 323*(7303), 42-46. doi: 10.1136/bmj.323.7303.42

Juni, P., Holenstein, F., Sterne, J., Bartlett, C., & Egger, M. (2002). Direction and impact of language bias in meta-analyses of controlled trials: empirical study. *International Journal of Epidemiology, 31*(1), 115-123. doi: 10.1093/ije/31.1.115

Juni, P., Witschi, A., Bloch, R., & Egger, M. (1999). The hazards of scoring the quality of clinical trials for meta-analysis. *Journal of the American Medical Association, 282*(11), 1054-1060. doi: doi:10.1001/jama.282.11.1054

Key, T. J., Allen, N. E., Verkasalo, P. K., & Banks, E. (2001). Energy balance and cancer: the role of sex hormones. *The Proceedings of the Nutrition Society, 60*(1), 81-89. doi: 10.1079/PNS200068

Key, T. J., Verkasalo, P. K., & Banks, E. (2001). Epidemiology of breast cancer. *The Lancet Oncology, 2*(3), 133-140. doi: 10.1016/S1470-2045(00)00254-0

Kim, C. J., Kang, D. H., & Park, J. W. (2009). A meta-analysis of aerobic exercise interventions for women with breast cancer. *Western Journal of Nursing Research, 31*(4), 437-461. doi: 10.1177/0193945908328473

King, R. J., & Robins, M. W. (2006). *Cancer biology* (3rd ed.). Harlow: Prentice Hall.

Kirshbaum, M. N. (2007). A review of the benefits of whole body exercise during and after treatment for breast cancer. *Journal of Clinical Nursing, 16*(1), 104-121. doi: 10.1111/j.1365-2702.2006.01638.x

Klein, S., Allison, D. B., Heymsfield, S. B., Kelley, D. E., Leibel, R. L., Nonas, C., & Kahn, R. (2007). Waist Circumference and Cardiometabolic Risk: a Consensus Statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Obesity (Silver Spring), 15*(5), 1061-1067. doi: 10.1038/oby.2007.632

Kroenke, C. H., Chen, W. Y., Rosner, B., & Holmes, M. D. (2005). Weight, weight gain, and survival after breast cancer diagnosis. *Journal of Clinical Oncology, 23*(7), 1370-1378. doi: 10.1200/JCO.2005.01.079

Lahmann, P. H., Hoffmann, K., Allen, N., van Gils, C. H., Khaw, K. T., Tehard, B., . . . Riboli, E. (2004). Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *International Journal of Cancer, 111*(5), 762-771. doi: 10.1002/ijc.20315

Lee, R. C., Wang, Z., Heo, M., Ross, R., Janssen, I., & Heymsfield, S. B. (2000). Total-body skeletal muscle mass: development and cross-validation of anthropometric prediction models. *American Journal of Clinical Nutrition, 72*(3), 796-803.

Lefebvre, C., Manheimer, E., & Glanville, J. (2011). Chapter 6: Searching for studies. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org.

Littman, A. J., Tang, M. T., & Rossing, M. A. (2010). Longitudinal study of recreational physical activity in breast cancer survivors. *Journal of Cancer Survivorship, 4*(2), 119-127. doi: 10.1007/s11764-009-0113-2

Livingstone, M. B., & Black, A. E. (2003). Markers of the validity of reported energy intake. *The Journal of Nutrition, 133*(Suppl 3), 895S-920S. Retrieved from http://jn.nutrition.org/content/133/3/895S

Livingstone, M. B., Prentice, A. M., Strain, J. J., Coward, W. A., Black, A. E., Barker, M. E., . . . Whitehead, R. G. (1990). Accuracy of weighed dietary records in studies of diet and health. *British Medical Journal, 300*(6726),

708-712. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1662510/

Lynch, B. M., Dunstan, D. W., Healy, G. N., Winkler, E., Eakin, E., & Owen, N. (2010). Objectively measured physical activity and sedentary time of breast cancer survivors, and associations with adiposity: findings from NHANES (2003-2006). *Cancer Causes Control, 21*(2), 283-288. doi: 10.1007/s10552-009-9460-6

Macmillan Cancer Support. (2011). Move More: Physical activity the underrated 'wonder drug'. Retrieved March 19, 2012, from http://www.macmillan.org.uk/Documents/AboutUs/Commissioners/Movemorereport.pdf

Macmillan Cancer Support. (2012). Treating breast cancer. Retrieved February 04, 2012, from http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Breast/Treatingbreastcancer/Treatingbreastcancer.aspx

Maddams, J. M. H., Møller, H., & Devane, C. (2008). Cancer prevalence in the UK, 2008. National Cancer Intelligence Network and Macmillan Cancer Support. Retrieved January 16, 2011, from http://www.ncin.org.uk/publications/reports/default.aspx

Makari-Judson, G., Judson, C. H., & Mertens, W. C. (2007). Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond

the first year. *The Breast Journal, 13*(3), 258-265. doi: 10.1111/j.1524-4741.2007.00419.x

Markes, M. (2010). Exercise as an intervention during breast cancer treatment. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 37-52). New York: Springer.

Markes, M., Brockow, T., & Resch, K. L. (2006). Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database of Systematic Reviews*(4), CD005001. doi: 10.1002/14651858.CD005001.pub2

Matthews, C. E., Wilcox, S., Hanby, C. L., Der Ananian, C., Heiney, S. P., Gebretsadik, T., & Shintani, A. (2007). Evaluation of a 12-week home-based walking intervention for breast cancer survivors. *Support Care Cancer, 15*(2), 203-211. doi: 10.1007/s00520-006-0122-x

McArdle, W. D., Katch, F. I., & Katch, V. L. (2001). *Exercise physiology, energy, nutrition & human performance* (5th ed.). Philadelphia: Lippincott Williams & Wilkins.

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Canadian Medical Association Journal, 175*(1), 34-41. doi: 10.1503/cmaj.051073

McTiernan, A. (Ed.). (2006). *Cancer Prevention and Management through Exercise and Weight Control*. Boca Raton; FL: CRC Press.

McTiernan, A., Tworoger, S. S., Ulrich, C. M., Yasui, Y., Irwin, M. L., Rajan, K. B., . . . Schwartz, R. S. (2004). Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. *Cancer Research, 64*(8), 2923-2928. Retrieved from doi:doi: 10.1158/0008-5472.CAN-03-3393

Mefferd, K., Nichols, J. F., Pakiz, B., & Rock, C. L. (2007). A cognitive behavioral therapy intervention to promote weight loss improves body composition and blood lipid profiles among overweight breast cancer survivors. *Breast Cancer Research and Treatment, 104*(2), 145-152. doi: 10.1007/s10549-006-9410-x

Mishra, S. I., Scherer, R. W., Geigle, P. M., Berlanstein, D. R., Topaloglu, O., Gotay, C. C., & Snyder, C. (2012). Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database of Systematic Reviews, 8*, CD007566. doi: 10.1002/14651858.CD007566.pub2

Mistry, M., Parkin, D. M., Ahmad, A. S., & Sasieni, P. (2011). Cancer incidence in the United Kingdom: projections to the year 2030. *British Journal of Cancer, 105*(11), 1795-1803. doi: 10.1038/bjc.2011.430

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gotzsche, P. C., Devereaux, P. J., . . . Altman, D. G. (2010). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *British Medical Journal, 340*, c869. doi: 10.1136/bmj.c869

Moher, D., Jadad, A. R., Nichol, G., Penman, M., Tugwell, P., & Walsh, S. (1995). Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. *Controlled Clinical Trials, 16*(1), 62-73. doi: 10.1016/0197-2456(94)00031-w

Moher, D., Jadad, A. R., & Tugwell, P. (1996). Assessing the quality of randomized controlled trials. Current issues and future directions. *International Journal of Technology Assessment in Healthcare, 12*(2).

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal, 339*, b2535. doi: 10.1136/bmj.b2535

Morin, S., Lix, L. M., Azimaee, M., Metge, C., Caetano, P., & Leslie, W. D. (2011). Mortality rates after incident non-traumatic fractures in older men and women. *Osteoporosis International, 22*(9), 2439-2448. doi: 10.1007/s00198-010-1480-2

National Institute for Health and Clinical Excellence. (2006). Obesity: the prevention, identification and management of overweight and obesity in adults and children. Clinical Guideline 432006. London: NICE.

Nichols, H. B., Trentham-Dietz, A., Egan, K. M., Titus-Ernstoff, L., Holmes, M. D., Bersch, A. J., . . . Newcomb, P. A. (2009). Body mass index before and after breast cancer diagnosis: associations with all-cause, breast cancer,

and cardiovascular disease mortality. *Cancer Epidemiology, Biomarkers & Prevention, 18*(5), 1403-1409. doi: 10.1158/1055-9965.EPI-08-1094

O'Connor, D., Green, S., & Higgins, J. P. T. (2011). Chapter 5: Defining the review question and developing criteria for including studies. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org

Pecorino, L. (2005). *Molecular biology of cancer; mechanisms, targets, and therapeutics.* Oxford: Oxford University Press.

Pierce, B. L., Neuhouser, M. L., Wener, M. H., Bernstein, L., Baumgartner, R. N., Ballard-Barbash, R., . . . Ulrich, C. M. (2009). Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors. *Breast Cancer Research and Treatment, 114*(1), 155-167. doi: 10.1007/s10549-008-9985-5

Pittler, M. H., Abbot, N. C., Harkness, E. F., & Ernst, E. (2000). Location bias in controlled clinical trials of complementary/alternative therapies. *Journal of Clinical Epidemiology, 53*(5), 485-489. doi: 10.1016/S08954356(99)002206

Plint, A. C., Moher, D., Morrison, A., Schulz, K., Altman, D. G., Hill, C., & Gaboury, I. (2006). Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *The Medical Journal of Australia, 185*(5), 263-267.

Rahnama, N., Nouri, R., Rahmaninia, F., Damirchi, A., & Emami, H. (2010). The effects of exercise training on maximum aerobic capacity, resting heart rate, blood pressure and anthropometric variables of postmenopausal women with breast cancer. *Journal of Research in Medical Sciences, 15*(2), 78-83.

Ravnskov, U. (1992). Cholesterol lowering trials in coronary heart disease: frequency of citation and outcome. *British Medical Journal, 305*(6844), 15-19.

Reeves, G. K., Pirie, K., Beral, V., Green, J., Spencer, E., Bull, D., & Million Women Study, C. (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *British Medical Journal, 335*(7630), 1134. doi: 10.1136/bmj.39367.495995.AE

Renehan, A. G., Tyson, M., Egger, M., Heller, R. F., & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet, 371*(9612), 569-578. doi: 10.1016/S0140-6736(08)60269-X

Rizzoli, R., Body, J. J., De Censi, A., Reginster, J. Y., Piscitelli, P., Brandi, M. L., . . . Osteoarthritis. (2012). Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper. *Osteoporosis International, January 2012 [Epub ahead of print]*. doi: 10.1007/s00198-011-1870-0

Rock, C. L., & Demark-Wahnefried, W. (2002). Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. *Journal of Clinical Oncology, 20*(15), 3302-3316. doi: 10.1200/JCO.2002.03.008

Rock, C. L., Flatt, S. W., Newman, V., Caan, B. J., Haan, M. N., Stefanick, M. L., . . . Pierce, J. P. (1999). Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. *Journal of the American Dietetic Association, 99*(10), 1212-1221. Retrieved from http://www.journals.elsevierhealth.com/periodicals/jand

Rogers, L. Q., McAuley, E., Anton, P. M., Courneya, K. S., Vicari, S., Hopkins-Price, P., . . . Hoelzer, K. (2012). Better exercise adherence after treatment for cancer (BEAT Cancer) study: rationale, design, and methods. *Contemporary Clinical Trials, 33*(1), 124-137. doi: 10.1016/j.cct.2011.09.004

Rooney, M., & Wald, A. (2007). Interventions for the management of weight and body composition changes in women with breast cancer. *Clinical Journal of Oncology Nursing, 11*(1), 41-52. doi: 10.1188/07.CJON.41-52

Saarto, T., Sievänen, H., Kellokumpu-Lehtinen, P., Nikander, R., Vehmanen, L., Huovinen, R., . . . Blomqvist, C. (2012). Effect of supervised and home exercise training on bone mineral density among breast cancer patients. A 12-month randomised controlled trial. *Osteoporosis International, 23*(5), 1601-1612. doi: 10.1007/s00198-011-1761-4

Saquib, N., Flatt, S. W., Natarajan, L., Thomson, C. A., Bardwell, W. A., Caan, B., . . . Pierce, J. P. (2007). Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. *Breast Cancer Research and Treatment, 105*(2), 177-186. doi: 10.1007/s10549-006-9442-2

Saxton, J., & Daley, A. (Eds.). (2010). *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life*. New York: Springer.

Schmitz, K. (2011). Physical activity and breast cancer survivorship. In K. Courneya & C. Friedenreich (Eds.), *Physical Activity and Cancer: Recent Results in Cancer Research (Vol. 186).* (pp. 189-209). Heidelberg: Springer.

Schmitz, K., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., . . . American College of Sports, M. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports and Exercise, 42*(7), 1409-1426. doi: 10.1249/MSS.0b013e3181e0c112

Schulz, K. F., Altman, D. G., Moher, D., & Group, C. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *British Medical Journal, 340*, c332. doi: 10.1136/bmj.c332

Schulz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American*

Medical Association,, 273(5), 408-412. doi: 10.1001/jama.1995.03520290060030

Song, F., Parekh-Bhurke, S., Hooper, L., Loke, Y. K., Ryder, J. J., Sutton, A. J., . . . Harvey, I. (2009). Extent of publication bias in different categories of research cohorts: a meta-analysis of empirical studies. [BMC Med Res Methodol]. *BMC Medical Research Methodology, 9*, 79. doi: 10.1186/1471-2288-9-79

Speck, R. M., Courneya, K. S., Masse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship, 4*(2), 87-100. doi: 10.1007/s11764-009-0110-5

Stern, J. M., & Simes, R. J. (1997). Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *British Medical Journal, 315*(7109), 640-645. doi: 10.1136/bmj.315.7109.640

Sterne, J. A. C., Egger, M., & Moher, D. (2011). Chapter 10: Addressing reporting biases. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]: The Cochrane Collaboration, 2011. Retrieved from www.cochrane-handbook.org.

Stevinson, C. (2010). Ready to change lifestyle? The feasibility of exercise interventions in cancer patients. In J. Saxton & A. Daley (Eds.), Exercise

and Cancer Survivorship: Impact on Health Outcomes and Quality of Life (pp. 211-222). New York: Springer.

Stevinson, C., & Lawlor, D. A. (2004). Searching multiple databases for systematic reviews: added value or diminishing returns? *Complementary Therapies in Medicine, 12*(4), 228-232. doi: 10.1016/j.ctim.2004.09.003

Stevinson, C., Lawlor, D. A., & Fox, K. R. (2004). Exercise interventions for cancer patients: systematic review of controlled trials. *Cancer Causes Control, 15*(10), 1035-1056. doi: 10.1007/s10552-004-1325-4

Tammemagi, C. M., Nerenz, D., Neslund-Dudas, C., Feldkamp, C., & Nathanson, D. (2005). Comorbidity and survival disparities among black and white patients with breast cancer. *Journal of the American Medical Association, 294*(14), 1765-1772. doi: 10.1001/jama.294.14.1765

Tramer, M. R., Reynolds, D. J., Moore, R. A., & McQuay, H. J. (1997). Impact of covert duplicate publication on meta-analysis: a case study. *British Medical Journal, 315*(7109), 635-640. doi: 10.1136/bmj.315.7109.635

Tredan, O., Bajard, A., Meunier, A., Roux, P., Fiorletta, I., Gargi, T., . . . Bachmann, P. (2010). Body weight change in women receiving adjuvant chemotherapy for breast cancer: a French prospective study. *Clinical Nutrition, 29*(2), 187-191. doi: 10.1016/j.clnu.2009.08.003

van Londen, G. J., Perera, S., Vujevich, K., Rastogi, P., Lembersky, B., Brufsky, A., . . . Greenspan, S. L. (2011). The impact of an aromatase inhibitor on

body composition and gonadal hormone levels in women with breast cancer. *Breast Cancer Research and Treatment, 125*(2), 441-446. doi: 10.1007/s10549-010-1223-2

van Tulder, M. W., Assendelft, W. J., Koes, B. W., & Bouter, L. M. (1997). Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine, 22*(20), 2323-2330.

Vance, V., Mourtzakis, M., McCargar, L., & Hanning, R. (2011). Weight gain in breast cancer survivors: prevalence, pattern and health consequences. *Obesity Reviews, 12*(4), 282-294. doi: 10.1111/j.1467-789X.2010.00805.x

Verhagen, A. P., de Vet, H. C., de Bie, R. A., Kessels, A. G., Boers, M., Bouter, L. M., & Knipschild, P. G. (1998). The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *Journal of Clinical Epidemiology, 51*(12), 1235-1241. doi: doi.org/10.1016/S0895-4356(98)00131-0

Visovsky, C. (2006). Muscle strength, body composition and physical activity in women receiving chemotherapy for breast cancer. *Integrative Cancer Therapies, 5*(3), 183-191.

von Elm, E., Poglia, G., Walder, B., & Tramer, M. R. (2004). Different patterns of duplicate publication: an analysis of articles used in systematic reviews. *Journal of the American Medical Association, 291*(8), 974-980. doi: 10.1001/jama.291.8.974

Waltman, N. L., Twiss, J. J., Ott, C. D., Gross, G. J., Lindsey, A. M., Moore, T. E., . . . Kupzyk, K. (2010). The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: a 24-month randomized controlled trial. *Osteoporosis International, 21*(8), 1361-1369. doi: 10.1007/s00198-009-1083-y

Wasnich, R. D., & Miller, P. D. (2000). Antifracture efficacy of antiresorptive agents are related to changes in bone density. [Meta-Analysis]. *The Journal of Clinical Endocrinology and Metabolism, 85*(1), 231-236. doi: 10.1210/jc.85.1.231

Wayne, S. J., Lopez, S. T., Butler, L. M., Baumgartner, K. B., Baumgartner, R. N., & Ballard-Barbash, R. (2004). Changes in dietary intake after diagnosis of breast cancer. *Journal of the American Dietetic Association, 104*(10), 1561-1568. doi: 10.1016/j.jada.2004.07.028

White, S. M., McAuley, E., Estabrooks, P. A., & Courneya, K. S. (2009). Translating physical activity interventions for breast cancer survivors into practice: an evaluation of randomized controlled trials. *Annals of Behavioral Medicine, 37*(1), 10-19. doi: 10.1007/s12160-009-9084-9

Wing, R. R., Matthews, K. A., Kuller, L. H., Meilahn, E. N., & Plantinga, P. L. (1991). Weight gain at the time of menopause. *Archives of Internal Medicine, 151*(1), 97-102. Retrieved from http://archinte.ama-assn.org

Winningham, M. L., MacVicar, M. G., Bondoc, M., Anderson, J. I., & Minton, J. P. (1989). Effect of aerobic exercise on body weight and composition in

patients with breast cancer on adjuvant chemotherapy. *Oncology Nursing Forum, 16*(5), 683-689.

Winters-Stone, K. M., Dobek, J., Nail, L., Bennett, J. A., Leo, M. C., Naik, A., & Schwartz, A. (2011). Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Research and Treatment, 127*(2), 447-456. doi: 10.1007/s10549-011-1444-z

Winters-Stone, K. M., Leo, M. C., & Schwartz, A. (2012). Exercise effects on hip bone mineral density in older, post-menopausal breast cancer survivors are age dependent. *Archives of Osteoporosis, March 2012 [Epub ahead of print]*. Retrieved from doi:10.1007/s11657-012-0071-6

Winters-Stone, K. M., Schwartz, A., & Nail, L. M. (2010). A review of exercise interventions to improve bone health in adult cancer survivors. *Journal of Cancer Survivorship, 4*(3), 187-201. doi: 10.1007/s11764-010-0122-1

World Health Organisation. (2004). Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. Technical Report Series, No.894 (pp. 265). Geneva : WHO.

Yancik, R., Wesley, M. N., Ries, L. A., Havlik, R. J., Edwards, B. K., & Yates, J. W. (2001). Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *Journal of the American Medical Association, 285*(7), 885-892. doi: 10.1001/jama.285.7.885

Yaw, Y. H., Shariff, Z. M., Kandiah, M., Mun, C. Y., Yusof, R. M., Othman, Z., . . . Hashim, Z. (2011). Weight changes and lifestyle behaviors in women after breast cancer diagnosis: a cross-sectional study. *BMC Public Health, 11*, 309. doi: 10.1186/1471-2458-11-309

Yeh, G. Y. (2008). Commentary on the Cochrane review of Tai Chi for rheumatoid arthritis. *Explore, 4*(4), 275-277. doi: 10.1016/j.explore.2008.04.011

Yeh, G. Y., Wang, C., Wayne, P. M., & Phillips, R. (2009). Tai chi exercise for patients with cardiovascular conditions and risk factors: A systematic review. *Journal of Cardiopulmonary Rehabilitation and Prevention, 29*(3), 152-160. doi: 10.1097/HCR.0b013e3181a33379

Appendix 1

Glossary

Glossary definitions that, unless otherwise stated apply throughout this MSc dissertation.

Aerobic exercise

Exercise that is performed in order to induce improvements in cardio-respiratory fitness, and is of such an intensity and duration that the predominate energy source is oxidative phosphorylation (McArdle, Katch, & Katch, 2001, p. 459).

Body fat percentage (BF%)

The amount of FM expressed as a percentage of the total BM (Heyward & Wagner, 2004, p. 5).

Body mass (BM)

A measure of the body's mass, also commonly referred to as body weight (Heyward & Wagner, 2004, p. 5).

Body mass index (BMI)

A measure of BM relative to height (World Health Organisation, 2004).

Bone mineral content (BMC)

The absolute amount of BMC (Heyward & Wagner, 2004, p. 5).

Breast cancer

A cancer that arises from a monoclonal origin in breast (mammary) tissue (Pecorino, 2005).

Appendix 1: Glossary /cont.

Breast cancer survivor (BCS)

Anyone diagnosed with breast cancer, from the point of diagnosis up until the end of their life, including all people living with a diagnosis of breast cancer and those who have recovered (J. K. Brown et al., 2003).

Cancer

A group of diseases characterised by unregulated cell growth, invasion of surrounding tissue and metastasis to parts of the body distinct from origin (King & Robins, 2006).

Cancer survivor

The American Cancer Association defines a cancer survivor as anyone who has been diagnosed with cancer, from the point of diagnosis up until the end of their life. This includes all people living with a diagnosis of cancer and those who have recovered (J. K. Brown et al., 2003).

Cluster randomised trial

A type of RCT in which clusters of people, rather than single individuals, are randomised to different interventions. For example, whole clinics or geographical locations may be randomised to receive a particular intervention (Centre for Reviews and Dissemination, 2009, pp. 11-12).

Exercise

Exercise is a subset of PA that is planned, structured and performed in order to improve one of more of the components of physical fitness (Caspersen et al., 1985).

Appendix 1: Glossary /cont.

Fat free mass (FFM)

All residual lipid-free tissues and chemicals in the body that remain after FM has been calculated including; water, muscle, bone, connective tissue and internal organs (Heyward & Wagner, 2004, p. 5).

Fat mass (FM)

The absolute amount of body fat; includes all extractable lipids from all tissues in the body (Heyward & Wagner, 2004, p. 5).

Healthy weight

A BMI of 18.5kg/m^2 to 24.9kg/m^2 (World Health Organisation, 2004).

Lean body mass (LBM)

Is similar to, but distinct from, FFM; LBM is FFM plus a small amount of essential lipids (Heyward & Wagner, 2004, p. 5).

Menopause

Technically refers to the final menstruation, however the menopause is not an abrupt event, but a gradual process which leads to the ceasing of menstruation (Key, Verkasalo, et al., 2001).

Overweight

A BMI of 25.0kg/m^2 to 29.9kg/m^2 (World Health Organisation, 2004).

Obese/Obesity

A BMI of >30kg/m^2 (World Health Organisation, 2004).

Appendix 1: Glossary /cont.

Parallel group trial

The most common type of RCT. A parallel group trial randomises participants to two or more groups, treats according to assignment, and compares the groups with respect to outcomes of interest. Participants are allocated to groups using both randomisation (allocation involves the play of chance) and concealment (ensures that the intervention that will be allocated cannot be known in advance) (Centre for Reviews and Dissemination, 2009, pp. 11-12).

Physical activity (PA)

Any bodily movement, produced by the contraction of skeletal muscle, which results in substantially increased EE (Caspersen et al., 1985).

Postmenopausal

Once menstruation has ceased for twelve months a woman is postmenopausal (Key, Verkasalo, et al., 2001).

Premenopausal

The fertile period of a women's life, when an egg is released from the ovaries each month; lasts from puberty to the menopause (Key, Verkasalo, et al., 2001).

Randomised controlled trial (RCT)

A RCT allocates participants, or groups of participants, to groups using randomisation and concealment (Centre for Reviews and Dissemination, 2009, pp. 11-12).

Appendix 1: Glossary /cont.

Randomised cross-over trial

A type of RCT in which participants receive all the interventions and the sequence of interventions are randomised. For example in a two arm cross-over trial, one group receives intervention A before intervention B, and the other group receives intervention B before intervention A (Centre for Reviews and Dissemination, 2009, pp. 11-12).

Resistance exercise

Exercise that is performed using BM or other resistance in order to induce increases in muscle strength; and is of such an intensity and duration that muscles are required to work close to their force-generating capacity (McArdle et al., 2001, p. 510).

Sarcoepenic BM gain / Sarcopenic Obesity

BM gain which is largely composed of FM, and occurs without the associated gains, or even losses in LBM (Heber et al., 1996).

Underweight

A BMI of <18.5kg/m^2 (World Health Organisation, 2004).

Waist Circumference (WC)

The horizontal measurement of the WC, where the waist is taken to be the point halfway between the lowest rib and the top of the hipbone (World Health Organisation, 2004).

Appendix 2

Summary of the types of breast cancer

Type of breast cancer	Classification	Description
Ductal carcinoma in situ (DCIS)	NST/NOS	Cancer cells are all contained inside the ducts of the breast and have not spread into the surrounding breast tissue. Early breast cancer with very little chance that any of the cells have spread to the lymph nodes or elsewhere in the body. About 4650 women are diagnosed with DCIS in the UK each year.
Lobular carcinoma in situ (LCIS)	NST/NOS	Lobular cancer in situ (LCIS) is not cancer; it is a type of lobular neoplasia. Some cells within the inner lining of the breast lobes have started to become abnormal. Having LCIS increases the risk of getting invasive breast cancer About 500 women are diagnosed with LCIS each year in the UK.
Invasive ductal breast cancer (ductal carcinoma)	NST/NOS	Cancer cells started in the cells that line the ducts of the breasts and have spread into the surrounding breast tissue. The most common type of breast cancer and accounts for 70-80% of all diagnosed breast cancers.
Invasive lobular breast cancer (lobular carcinoma)	Special type	Cancer cells started in the cells that line the lobules or lobes of the breast and have spread into the surrounding breast tissue. 10-15% of breast cancers are invasive lobular carcinoma.
Inflammatory breast cancer	Special type	Cancer cells block the smallest lymph channels in the breast causing the breast tissue to become inflamed. A rare type of breast cancer, only 1-4% of breast cancers are inflammatory.
Paget's disease	Special type	Paget's disease is not cancer. Begins in the nipple or the areola and is a sign that there is a breast cancer in the breast tissues behind the nipple. A rare disease that is associated with breast cancer and is found in 1-2% of women diagnosed breast cancers. 50% of women diagnosed with Paget's disease have a lump behind the nipple, In 9 out of 10 cases; this is an invasive breast cancer.
Medullary breast cancer	special type	Medullary breast cancer tumors contain white blood cells, the cancer cells are bigger than other types of breast cancer cells, a clear boundary can be seen between the tumour and the normal tissue. It is more common in women who have inherited a faulty BRCA 1 gene. About 5% of breast cancers are medullary breast cancers.

Appendix 2: Summary of the types of breast cancer /cont.

Type of breast cancer	Classification	Description
Rare types of breast cancer • Medullary breast cancer • Mucinous (mucoid or colloid) breast cancer • Tubular breast cancer • Adenoid cystic carcinoma • Metaplastic breast cancer • Angiosarcoma of the breast • Lymphoma of the breast • Basal type breast cancer • Phyllodes / cytosarcoma phyllodes • Papillary breast cancer	special type	These special type breast cancers have cells with particular features under the microscope. Each type accounts for fewer than 1% of breast cancers.
oestrogen receptor positive (ER positive)	special type	ER positive breast cancers have a large number of ER on their surface. Oestrogen attaches to these receptors and stimulates the tumour to grow and divide. Hormone therapy may be used to treat an ER positive breast cancer so as to reduce oestrogen in the body block its stimulating effect on the growth of the this type of breast cancer.
progesterone receptor positive (PR positive)	special type	PR positive breast cancers have a large number of PR on their surface. Progesterone attaches to these receptors and stimulates the tumour to grow and divide. Hormone therapy may be used to treat a PR positive breast cancer so as to reduce progesterone in the body and block its stimulating effect on the growth of this type of breast cancer.
Human epidermal growth factor receptor 2 positive (HER2 positive)	special type	HER2 positive breast cancers have a large number of HER2 receptors on their surface. Human epidermal growth factor attaches to these receptors and stimulates the tumour to grow and divide. Herceptin by used in the treatment of HER2 positive breast cancer as it attaches to HER2 receptors on the surface of breast cancer cells stopping the cancer cells from dividing and growing.
Triple receptor negative	NST/NOS	Triple receptor negative breast cancers do not have ER, PR or HER2 receptors on their surface.

NST = no special type; NOS = not otherwise specified; Adapted from Cancer Research UK (2011d)

Appendix 3

The Tumour, Node, Metastasis (TNM) system of breast cancer staging

TNM Stage	Description
T stages	**T stands for tumour and it denotes of the size of the tumour**
TX	The tumour size cannot be assessed
T1	The tumour is no more than 2 cm across
• T1mic	• Microscopically the cancer cells spread less than 0.1cm into surrounding tissue (microinvasion)
• T1a	• The tumour is more than 0.1 cm but not more than 0.5 cm
• T1b	• The tumour is more than 0.5 cm but not more than 1 cm
• T1c	• The tumour is more than 1 cm but not more than 2 cm
T2	The tumour is more than 2 cm, but no more than 5 cm across
T3	The tumour is bigger than 5 cm across
T4	
• T4a	• The tumour has spread into the chest wall
• T4b	• The tumour has spread into the skin
• T4c	• The tumour is fixed to both the skin and the chest wall
• T4d	• Inflammatory carcinoma, the overlying skin is red, swollen and painful to the touch
N stages	**N stands for node and it denotes whether the cancer has spread to nearby lymph nodes and which nodes are affected**
NX	The lymph nodes cannot be assessed (e.g. if they were previously removed)
NO	No cancer cells found in any nearby nodes
N1	Cancer cells are in the upper levels of lymph nodes in the armpit but the nodes are not stuck to surrounding tissues
N2	
• N2a	• There are cancer cells in the lymph nodes in the armpit, which are stuck to each other and to other structures
• N2b	• There are cancer cells in the lymph nodes behind the breast bone (the internal mammary nodes, which have either been seen on a scan or felt by the doctor. There is no evidence of cancer in lymph nodes in the armpit
N3	
• N3a	• There are cancer cells in lymph nodes below the collarbone
• N3b	• There are cancer cells in lymph nodes in the armpit and under the breast bone
• N3c	• There are cancer cells in lymph nodes above the collarbone
M stages	**M stands for metastasis and denotes whether the cancer has spread to other parts of the body**
M0	There is no sign of cancer spread
M1	There are signs the cancer has spread to another part of the body, apart from the breast and lymph nodes under the arm

Adapted from Cancer Research UK (2011c)

Appendix 4
The number system of breast cancer staging

Number Stage	Description
Stage 1 breast cancer	The tumour is no more than 2 cm across (T1) There are no cancer cells in the lymph nodes in the armpit The cancer has not spread anywhere else
Stage 2A breast cancer	The tumour is less than 2 cm, the lymph nodes under the arm contain cancer but are not stuck to each other and the cancer has not spread **or** The tumour is less than 5 cm, there are no cancer cells in the lymph nodes in the armpit and the cancer has not spread **or** Although no tumour is seen in the breast, the lymph nodes under the arm contain cancer cells but are not stuck together or to other structures, and there is no sign of spread to other parts of the body
Stage 2B breast cancer	The tumour is less than 5 cm and the lymph nodes under the arm contain cancer cells but are not stuck to each other, and the cancer has not spread **or** The tumour is bigger than 5 cm across, there are no cancer cells in the lymph nodes in the armpit and the cancer has not spread
Stage 3A breast cancer	Although no tumour is seen in the breast, the lymph nodes under the arm contain cancer cells and are stuck together or to other structures, but there is no sign of cancer spread **or** The tumour is 5 cm or less, the lymph nodes in the armpit contain cancer cells and are stuck to each other, but the cancer has not spread elsewhere **or** The tumour is more than 5 cm, the lymph nodes in the armpit contain cancer cells and may be stuck together, but there is no further spread
Stage 3B breast cancer	The tumour is fixed to the skin or chest wall, the lymph nodes may or may not contain cancer cells, but there is no further spread
Stage 3C breast cancer	The tumour can be any size and has spread to lymph nodes in the armpit and under the breast bone, or to nodes above or below the collarbone, but there is no further spread
Stage 4 breast cancer	The tumour can be any size The lymph nodes may or may not contain cancer cells The cancer has spread (metastasised) to other parts of the body such as the lungs, liver or bones

Adapted from Cancer Research UK (2011b)

Appendix 5
Summary of treatments for breast cancer and associated side effects

Type of treatment	Aim / Description	Side Effects
Breast surgery	To remove cancerous tissue from the breast	• Scaring • Emotional symptoms; anxiety, depression and low confidence associated with coping with a changed appearance • Pain or stiffness in the breast shoulder or arm • Peripheral neuropathy - numbness and tingling in the upper arm • Cording - an uncomfortable sensation that feels like a tight cord running from the armpit to the back of the hand - possibly due to hardened lymph vessels • Changes in arm/shoulder movement and strength • Lymphoedema - a swelling of the arm on the affected side. Women who have all or a large number of lymph nodes in the armpit removed are more at risk
Breast conserving surgery (wide local excision or lumpectomy)	To remove the breast tumour and a small amount of breast tissue around the tumour, called a margin.	
Mastectomy	To remove the whole of the breast tissue and possibly the lymph nodes (axillary nodes) in the armpit on the same side. Indicated for very large tumours, or where the tumour is relatively large in comparison to the size of the breast, or where the cancer is in more than one area of the breast.	
Axillary surgery	To determine if lymph nodes in the axilla have been affected, and if so to remove them.	
Sentinel node biopsy	To remove the first nodes that any cancer cells in the breast would reach if they were to spread and perform microscopic examination to check look for the presence of cancer cells.	
Axillary node sampling	To remove at least four lymph nodes from the lower level of the axilla and perform microscopic examination to check look for the presence of cancer cells.	
Axillary node clearance	To remove all the lymph nodes in the armpit to reduce the risk of cancer spreading beyond the breast. Indicated when cancer cells are found in the lymph nodes following sentinel node biopsy or axillary sampling. Avoids the need for radiotherapy to the axilla.	
Reconstructive breast surgery	To improve the appearance of the breast either at the same time as mastectomy (immediate reconstruction) or at some time after mastectomy (delayed reconstruction)	
Radiotherapy	To reduce the likelihood of cancer returning by using radiation to destroy any cancer cells remaining after surgery. May be given to the whole breast, just the tumour area of the breast, the chest wall, the axilla.	• Reddening and soreness of the skin • Changes in appearance and texture of the breast • Telangiectasia – damage to the small blood vessels in the skin • Fatigue • Nausea • Lymphoedema - a swelling of the arm on the affected side following radiotherapy to the armpit • Inflammation of the lung (radiation pneumonitis) causing breathlessness, dry cough or chest pain • Peripheral neuropathy • Rarely causes heart problems • Rarely causes a hardening and thickening (fibrosis) of the lung tissue • Rarely weakens the ribs in the treated area, making them more likely to fracture
External radiotherapy	Delivered from outside the body, through the skin, using high energy x-rays.	
Internal radiotherapy (interstitial brachytherapy)	Delivered via radioactive wires or needles inserted into the body for a short time	

Appendix 5: Summary of treatments for breast cancer and associated side effects /cont.

Type of treatment	Aim / Description	Side Effects
Chemotherapy Cyclophosphamide Epirubicin Fluorouracil (5FU) Methotrexate Mitomycin Mitozantrone Doxorubicin Docetaxel (Taxotere) Gemcitabine (Gemzar) **Chemotherapy Regimes** **CMF** (cyclophosphamide,methotrexate, fluorouracil) **FEC** (epirubicin, cyclophosphamide, fluorouracil) **FEC-T** FEC followed by taxotere) **E-CMF** (epirubicin, followed by CMF) **AC** (doxorubicin (adriamycin), cyclophosphamide) **EC** (epirubicin, cyclophosphamide) **MMM** (methotrexate, mitozantrone, mitomycin) **MM** (methotrexate, mitozantrone) **Neoadjuvant chemotherapy** **Adjuvant chemotherapy**	To reduce the likelihood of cancer returning by using anticancer (cytotoxic) drugs to destroy any cancer cells that may have spread beyond the breast and axillary lymph nodes, or when surgery to remove the cancer is not possible/appropriate. Chemotherapy is a systemic treatment; it affects healthy cells as well as cancer cells. The dose of chemotherapy is calculated to have the most impact on cancer cells and the least effect on healthy cells. Chemotherapy is given as a course of treatment, lasting several weeks or months. The course is divided into smaller units called cycles. Combination (multi-agent) chemotherapy is generally more effective than being treated with just one drug. The way in which chemotherapy is given (the particular drugs and when they are administered) is called a regimen. Taxanes are a type of chemotherapy drug that are often used in the treatment of breast cancer. The most commonly used is docetaxel (Taxotere). Anthracyclines are a type of chemotherapy drug that are commonly included in chemotherapy regimes. The most commonly used are doxorubicin (Adriamycin) and epirubicin. Given before surgery to shrink a breast tumour to allow breast conserving surgery to be carried out rather than a mastectomy, or to make an operation feasible. Given after surgery to reduce the likelihood of cancer returning by destroying any cancer cells that may have spread beyond the breast and axillary lymph nodes	• Neutropenia (reduced number of white blood cells) leading to increased risk of infection. • Reduction in platelets, reduced blood clotting ability causing bruising or bleeding e.g. nosebleeds, bleeding gums, rashes on the skin. • Anaemia (reduced number of red blood cells), reduced oxygen carrying capacity leading to fatigue and breathlessness. • Nausea or Vomiting • Fatigue • Dizziness • Pain in joints or muscles • Flu-like symptoms • Hair loss • Taste changes • Sore mouth, dry mouth and ulcers • Conjunctiva (inflammation of the lining of the eyelids) Skin rashes, dry itchy skin • Areas of skin previously treated with radiotherapy may become red and sore (radiation recall) • Extravasation (Leakage into the tissue around the vein) causing tissue damage, redness and swelling • Palmar plantar (soreness and redness of the palms of the hands and soles of the feet • Sun sensitivity • Nail changes • Fluid retention causing gain weight, swelling of ankles and legs • Peripheral neuropathy • Bladder irritation • Diarrhoea • Changes in liver function • Changes in heart function • Allergic reaction • Increased risk of thrombosis • Anxiety, stress and depression • Cognitive problems • Temporary loss of menstruation • Menopause, Menopausal symptoms • Weight gain • Menopause related osteoporosis • Harm to a developing foetus

Appendix 5: Summary of treatments for breast cancer and associated side effects /cont.

Type of treatment	Aim / Description	Side Effects
Hormone Therapy **Aromatase inhibitors (AIs)** anastrozole (Arimidex®) letrozole (Femara®) exemestane (Aromasin®) **Anti oestrogens (AOs)** tamoxifen **Pituitary down-regulators** goserelin (Zoladex®) **Surgery** ovarian ablation	To shrink an oestrogen receptor positive (ER positive) tumor before surgery To reduce the chance of an ER positive breast cancer coming back The type of hormone therapy used depends on; menopausal status, the risk of the cancer returning and the likely side effects of the drugs used. Postmenopausal women may be treated with an aromatase inhibitor e.g. anastrozole (Arimidex®), letrozole (Femara®) or exemestane (Aromasin®) and or the anti oestrogen drug tamoxifen. Premenopausal women may be treated with tamoxifen, a pituitary down-regulator drug to suppress oestrogen production from the ovaries e.g. goserelin (Zoladex®), surgery to remove the ovaries (ovarian ablation) or a combination of tamoxifen with either Zoladex or ovarian ablation In premenopausal women, some hormonal treatments bring on a temporary or permanent menopause Treatment with hormonal therapy may continue for several years.	• Temporary loss of menstruation • Menopause • Menopausal symptoms (hot flushes and sweats, joint pain, lowered sex drive) • Osteoporosis • Tumour Flare – a temporary increase in tumour size and symptoms during the first few days of Zoladex treatment • Skin rashes • Joint pain • Fatigue • Weight gain • Vaginal bleeding • Harm to developing foetus • Slightly increased risk of endometrial cancer • Increased risk of thrombosis
Biological Therapy **Monoclonal antibody treatment** trastuzumab (Herceptin®)	To reduce the risk of human epidermal growth factor receptor 2 (HER2) positive breast cancers returning HER2 positive breast cancers have a large number of HER2 receptors on their surface Herceptin works by attaching to HER2 receptors on the surface of breast cancer cells stopping the cancer cells from dividing and growing. It also works by encouraging the body's own immune cells to destroy the cancer cells. It is sometimes referred to as a targeted therapy as it targets the cancer cells Treatment with Herceptin usually lasts for 1 year	• Flu-like symptoms (headache, high temperature (fever) and chills, feeling sick or being sick) • Allergic reaction (a skin rash, itching, wheezing, difficulty breathing, and breathlessness) • Diarrhoea • Headaches • Nausea • May cause heart problems and it is therefore not recommended for women with history of heart disease or high blood pressure

Adapted from Breakthrough Breast Cancer (2009) and Macmillan Cancer Support (2012)

Appendix 6

Completed PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**ii; 1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**ii-iii**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**1-2; 3-26**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**26-28**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**na**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**39-43**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**35-39; XV-XXI**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**XV-XXI**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**39-43**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**49-50; XXX-XXXIII**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**I-V**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**43-49**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**49; XXV-XXVIII**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**na**

Appendix 6: Completed PRISMA checklist /cont.

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**40-42**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**na**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**51**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**53-69**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**70-71; XXIX**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**53-69**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**na**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**71**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**na**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**72-90**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**91-93**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**72-92; 94-95**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**na**

Na = not applicable The PRISMA checklist taken from Moher et al. (2009)

Appendix 7

Full details of electronic bibliographical database searches

Database	Fields Searched	Search	Limits Applied	No. of records 30/04/2012	No. of records 04/07/2012
MEDLINE	all	(Breast AND Cancer OR "Breast Neoplasm" OR "Breast Carcinoma" OR "Breast Tumor" OR "Breast Tumour" OR "Mammary Cancer" OR "Mammary Neoplasm" OR "Mammary Carcinoma" OR "Mammary Tumor" OR" Mammary Tumour" OR" Ductal Carcinoma in Situ" OR "Lobular Carcinoma in Situ" OR "Invasive Ductal Breast Cancer" OR "Ductal Carcinoma" OR "Invasive Lobular Breast Cancer" OR "Lobular Carcinoma" OR "Invasive Breast Cancer" OR "Breast Cancer Patient" OR "Breast Cancer Survivors" OR "Breast Cancer Survivorship" OR "Breast Cancer Recovery" OR "Breast Cancer Treatment") AND (Exercise OR "Exercise Intervention" OR "Exercise Program" OR "Exercise Programme" OR "Exercise Training" OR "Exercise Therapy" OR "Rehabilitation" OR "Physical Activity" OR "Physical Activity Intervention" OR "Physical Therapy" OR "Physical Fitness" OR "Aerobic Exercise" OR "Aerobic Training" OR "Aerobics" OR "Resistance Exercise" OR "Resistance Training" OR "Weight Training" OR "Weight Lifting" OR "Muscle Strengthening" OR "Walking" OR "Running" OR "Jogging" OR "Cycling" OR "Rowing" OR "Racing")	Publication Date from 1989/01/01 Humans Female, All Adult: 19+ yrs	**1914**	**51**
The Cochrane Library	all	(Breast AND Cancer OR "Breast Neoplasm" OR "Breast Carcinoma" OR "Breast Tumor" OR "Breast Tumour" OR "Mammary Cancer" OR "Mammary Neoplasm" OR "Mammary Carcinoma" OR "Mammary Tumor" OR" Mammary Tumour" OR" Ductal Carcinoma in Situ" OR "Lobular Carcinoma in Situ" OR "Invasive Ductal Breast Cancer" OR "Ductal Carcinoma" OR "Invasive Lobular Breast Cancer" OR "Lobular Carcinoma" OR "Invasive Breast Cancer" OR "Breast Cancer Patient" OR "Breast Cancer Survivors" OR "Breast Cancer Survivorship" OR "Breast Cancer Recovery" OR "Breast Cancer Treatment") AND (Exercise OR "Exercise Intervention" OR "Exercise Program" OR "Exercise Programme" OR "Exercise Training" OR "Exercise Therapy" OR "Rehabilitation" OR "Physical Activity" OR "Physical Activity Intervention" OR "Physical Therapy" OR "Physical Fitness" OR "Aerobic Exercise" OR "Aerobic Training" OR "Aerobics" OR "Resistance Exercise" OR "Resistance Training" OR "Weight Training" OR "Weight Lifting" OR "Muscle Strengthening" OR "Walking" OR "Running" OR "Jogging" OR "Cycling" OR "Rowing" OR "Racing")	Publication Date from: 1989/01/01	**914**	**12**
CINHAL	all	(Breast AND Cancer OR "Breast Neoplasm" OR "Breast Carcinoma" OR "Breast Tumor" OR "Breast Tumour" OR "Mammary Cancer" OR "Mammary Neoplasm" OR "Mammary Carcinoma" OR "Mammary Tumor" OR" Mammary Tumour" OR" Ductal Carcinoma in Situ" OR "Lobular Carcinoma in Situ" OR "Invasive Ductal Breast Cancer" OR "Ductal Carcinoma" OR "Invasive Lobular Breast Cancer" OR "Lobular Carcinoma" OR "Invasive Breast Cancer" OR "Breast Cancer Patient" OR "Breast Cancer Survivors" OR "Breast Cancer Survivorship" OR "Breast Cancer Recovery" OR "Breast Cancer Treatment") AND (Exercise OR "Exercise Intervention" OR "Exercise Program" OR "Exercise Programme" OR "Exercise Training" OR "Exercise Therapy" OR "Rehabilitation" OR "Physical Activity" OR "Physical Activity Intervention" OR "Physical Therapy" OR "Physical Fitness" OR "Aerobic Exercise" OR "Aerobic Training" OR "Aerobics" OR "Resistance Exercise" OR "Resistance Training" OR "Weight Training" OR "Weight Lifting" OR "Muscle Strengthening" OR "Walking" OR "Running" OR "Jogging" OR "Cycling" OR "Rowing" OR "Racing")	Publication Date from: 1989/01/01 Female All Adult	**730**	**34**

Appendix 7

Full details of electronic bibliographical database searches /cont.

Database	Fields Searched	Search	Limits Applied	No. of records 30/04/2012	No. of records 04/07/2012
PROQUEST	all	all("Breast Cancer" OR "Breast Neoplasm" OR "Breast Carcinoma" OR "Breast Tumor" OR "Breast Tumour" OR "Mammary Cancer" OR "Mammary Neoplasm" OR "Mammary Carcinoma" OR "Mammary Tumor" OR" Mammary Tumour" OR" Ductal Carcinoma in Situ" OR "Lobular Carcinoma in Situ" OR "Invasive Ductal Breast Cancer" OR "Ductal Carcinoma" OR "Invasive Lobular Breast Cancer" OR "Lobular Carcinoma" OR "Invasive Breast Cancer" OR "Breast Cancer Patient" OR "Breast Cancer Survivors" OR "Breast Cancer Survivorship" OR "Breast Cancer Recovery" OR "Breast Cancer Treatment") AND all(("Exercise" OR "Exercise Intervention" OR "Exercise Program" OR "Exercise Programme" OR "Exercise Training" OR "Exercise Therapy" OR "Rehabilitation" OR "Physical Activity" OR "Physical Activity Intervention" OR "Physical Therapy" OR "Physical Fitness" OR "Aerobic Exercise" OR "Aerobic Training" OR "Aerobics" OR "Resistance Exercise" OR "Resistance Training" OR "Weight Training" OR "Weight Lifting" OR "Muscle Strengthening" OR "Walking" OR "Running" OR "Jogging" OR "Cycling" OR "Rowing" OR "Racing"))	Publication Date from:1 989/01/01 Female Adult (19-44 yrs; 65+ yrs; 80+ yrs; Middle aged 45-64 years)	**640**	**12**
Sports Discus	all	(Breast AND Cancer OR "Breast Neoplasm" OR "Breast Carcinoma" OR "Breast Tumor" OR "Breast Tumour" OR "Mammary Cancer" OR "Mammary Neoplasm" OR "Mammary Carcinoma" OR "Mammary Tumor" OR" Mammary Tumour" OR" Ductal Carcinoma in Situ" OR "Lobular Carcinoma in Situ" OR "Invasive Ductal Breast Cancer" OR "Ductal Carcinoma" OR "Invasive Lobular Breast Cancer" OR "Lobular Carcinoma" OR "Invasive Breast Cancer" OR "Breast Cancer Patient" OR "Breast Cancer Survivors" OR "Breast Cancer Survivorship" OR "Breast Cancer Recovery" OR "Breast Cancer Treatment") AND (Exercise OR "Exercise Intervention" OR "Exercise Program" OR "Exercise Programme" OR "Exercise Training" OR "Exercise Therapy" OR "Rehabilitation" OR "Physical Activity" OR "Physical Activity Intervention" OR "Physical Therapy" OR "Physical Fitness" OR "Aerobic Exercise" OR "Aerobic Training" OR "Aerobics" OR "Resistance Exercise" OR "Resistance Training" OR "Weight Training" OR "Weight Lifting" OR "Muscle Strengthening" OR "Walking" OR "Running" OR "Jogging" OR "Cycling" OR "Rowing" OR "Racing")	Publication Date from: 1989/01/01	**761**	**8**
PEDRO	(ab/title)	See Appendix 8	Publication Date from 1989/01/01	**1196**	**43**
Total				**6155**	**160**

Appendix 8

Full details of electronic bibliographical PEDro searches

Search Number	**Search terms entered into the PEDRO database** Searches limits; ab/title and Publication Date from 1989/01/01 to 2012/06/30	No. of Records 01/05/2012	No. of Records 04/07/2012
1	Breast AND Cancer AND Exercise	212	6
2	Breast AND Cancer AND Training	77	3
3	Breast AND Cancer AND Rehabilitation	41	2
4	Breast AND Cancer AND Physical Activity	74	3
5	Breast AND Cancer AND Fitness	30	0
6	Breast AND Cancer AND Aerobic	81	2
7	Breast AND Cancer AND Resistance	47	1
8	Breast AND Cancer AND Weight Training	21	1
9	Breast AND Cancer AND Weight Lifting	2	0
10	Breast AND Cancer AND Muscle Strength	19	0
11	Breast AND Cancer AND Walking	32	1
12	Breast AND Cancer AND Running	2	1
13	Breast AND Cancer AND Jogging	1	0
14	Breast AND Cancer AND Cycling	3	0
15	Breast AND Cancer AND Rowing	0	0
16	Breast AND Cancer AND Racing	0	0
17	Breast Neoplasm	2	0
18	Breast Carcinoma	6	0
19	Breast Tumor	14	0
20	Breast Tumour	3	0
21	Mammary Cancer	3	0
22	Mammary Neoplasm	0	0
23	Mammary Carcinoma	1	0
24	Mammary Tumor	0	0
25	Mammary Tumour	0	0
26	Ductal Carcinoma in Situ	0	0
27	Lobular Carcinoma in Situ	0	0
28	Invasive Ductal Breast Cancer	0	0
29	Ductal Carcinoma	0	0
30	Invasive Lobular Breast Cancer	0	0
31	Lobular Carcinoma	0	0
32	Invasive Breast Cancer	2	0
33	Breast Cancer Patient	192	7
34	Breast Cancer Survivors	98	6
35	Breast Cancer Survivorship	7	0
36	Breast Cancer Recovery	16	1
37	Breast Cancer Treatment	210	10
TOTAL		**1196**	**43**

Appendix 9

Full details of the ZETOC database searches

Search Number	Search terms entered into the ZETOC database Searches limits; Conference only; Publication Year from 1989 – 2012	No. of Records 04/05/2012	No. of Records 04/07/2012
1	Breast AND Cancer AND Exercise	15	0
2	Breast AND Cancer AND Training	25	0
3	Breast AND Cancer AND Rehabilitation	11	0
4	Breast AND Cancer AND Physical Activity	15	0
5	Breast AND Cancer AND Fitness	1	0
6	Breast AND Cancer AND Aerobic	4	0
7	Breast AND Cancer AND Resistance	1	0
8	Breast AND Cancer AND Weight Training	0	0
9	Breast AND Cancer AND Weight Lifting	0	0
10	Breast AND Cancer AND Muscle Strength	1	0
11	Breast AND Cancer AND Walking	0	0
12	Breast AND Cancer AND Running	0	0
13	Breast AND Cancer AND Jogging	0	0
14	Breast AND Cancer AND Cycling	0	0
15	Breast AND Cancer AND Rowing	0	0
16	Breast AND Cancer AND Racing	0	0
17	“Breast Neoplasm”	3	0
18	“Breast Carcinoma”	390	0
19	“Breast Tumor”	193	0
20	“Breast Tumour”	23	0
21	“Mammary Cancer”	58	0
22	“Mammary Neoplasm”	0	0
23	“Mammary Carcinoma”	94	0
24	“Mammary Tumor”	74	0
25	“Mammary Tumour”	11	0
26	“Ductal Carcinoma in Situ”	143	0
27	“Lobular Carcinoma in Situ”	10	0
28	“Invasive Ductal Breast Cancer”	2	0
29	“Ductal Carcinoma”	176	0
30	“Invasive Lobular Breast Cancer”	1	0
31	“Lobular Carcinoma”	33	0
32	“Invasive Breast Cancer”	93	0
33	“Breast Cancer Survivor*”	73	0
34	“Breast Cancer Recovery”	8	0
35	“Breast Cancer Treatment”	147	0
TOTAL		**1605**	**0**

Appendix 10

Full details of the SCIRUS database searches

Search Number	**Search terms entered into the SCIRUS database** Searches limits; Title; preferred web sources; any information type; publication year from 1989 – 2012	No. of Records 04/05/2012	No. of Records 04/07/2012
1	Breast AND Cancer AND Exercise	**38**	**1**
2	Breast AND Cancer AND Training	**17**	**0**
3	Breast AND Cancer AND Rehabilitation	**13**	**2**
4	Breast AND Cancer AND Physical Activity	**31**	**3**
5	Breast AND Cancer AND Fitness	**3**	**0**
6	Breast AND Cancer AND Aerobic	**2**	**0**
7	Breast AND Cancer AND Resistance Training	**4**	**0**
8	Breast AND Cancer AND Weight Training	**0**	**0**
9	Breast AND Cancer AND Weight Lifting	**1**	**0**
10	Breast AND Cancer AND Muscle Strength	**0**	**0**
11	Breast AND Cancer AND Walking	**2**	**0**
12	Breast AND Cancer AND Running	**1**	**0**
13	Breast AND Cancer AND Jogging	**0**	**0**
14	Breast AND Cancer AND Cycling	**0**	**0**
15	Breast AND Cancer AND Rowing	**0**	**0**
16	Breast AND Cancer AND Racing	**0**	**0**
17	Breast Cancer Survivor*	**109**	**1**
18	Breast Cancer Recovery	**15**	**0**
TOTAL		**204**	**25**

Appendix 11

Full details of the handsearched book chapters

Book	Chapters searched	No. of Records
Courneya, K. S., & Friedenreich, C. M. (Eds.). (2011). *Physical Activity and Cancer: Recent Results in Cancer Research* (Vol. 186). Heidelberg: Springer.	Schmitz, K. (2011). Physical activity and breast cancer survivorship. In K. Courneya & C. Friedenreich (Eds.), *Physical Activity and Cancer: Recent Results in Cancer Research (Vol. 186).* (pp. 189-209). Heidelberg: Springer.	**72**
Irwin, M. L. (Ed.). (2012). *ACSM's Guide to Exercise and Cancer Survivorship*. Champaign; IL: Human Kinetics.	Campbell, K. (2012). Benefits of physical activity after a cancer diagnosis. In M. Irwin (Ed.), *ACSM's Guide to Exercise and Cancer Survivorship* (pp. 49-71). Champaign; IL: Human Kinetics.	**42**
McTiernan, A. (Ed.). (2006). Cancer Prevention and Management through Exercise and Weight Control. Boca Raton; FL: CRC Press.	Harvie, M., & Howell, A. (2006). Incorporating weight control into management of patients with early breast cancer in the UK. In A. McTiernan (Ed.), *Cancer Prevention and Management through Exercise and Weight Control* (pp. 535-560). Boca Raton; FL: CRC Press.	**7**
Saxton, J., & Daley, A. (Eds.). (2010). Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life. New York: Springer.	Markes, M. (2010). Exercise as an intervention during breast cancer treatment. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 37-52). New York: Springer.	**24**
	Crank, H., & Daley, A. (2010). Exercise after treatment for breast cancer: Effects on quality of life. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 53-72). New York: Springer.	**43**
	Harvie, M. N. (2010). The importance of controlling body weight after a diagnosis of breast cancer: the role of diet and exercise in breast cancer patient management. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 73-96). New York: Springer.	**14**
	Irwin, M. (2010). The biological mechanisms by which physical activity might have a impact on outcome/prognosis after a breast cancer diagnosis. In J. Saxton & A. Daley (Eds.), *Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life* (pp. 97-112). New York: Springer.	**11**
	Stevinson, C. (2010). Ready to change lifestyle? The feasibility of exercise interventions in cancer patients. In J. Saxton & A. Daley (Eds.), Exercise and Cancer Survivorship: Impact on Health Outcomes and Quality of Life (pp. 211-222). New York: Springer.	**31**
Total		**237**

Appendix 12

Full details of the specific online journals that were handsearched

Journal	Access Method	Details of Issues Searched	Dates search performed	No. Records Retrieved
British Journal of Sports Medicine	University of Chester Subscription via http://bjsm.bmj.com	Full Text - Vol.23(1) Mar 1989 to Vol. 46(8) Jun 2012	12/05/2012 05/07/2012	**4**
Journal of Cancer Survivorship	University of Chester Subscription via ProQuest	Full Text - Vol. 1(2) Jun 2007 to Vol.5 (1) Mar 2011 Title and Abs - Vol.5(2) Jun 2011 to Vol. 6(2) Jun 2012	08/05/2012 05/07/2012	**16**
Journal of Clinical Oncology	Freely available content via http://jco.ascopubs.org	Title and Abs - Vol.7(1) Jan 1989 to Vol.30(18) Jun 2012	08-10/05/2012 05/07/2012	**67**
Cancer, Epidemiology, Biomarkers & Prevention	Freely available content via http://cebp.aacrjournals.org	Full text - Vol.1(1) Nov1991 to Vol.20(5) May 2011 Title and Abs - Vol.20(6) Jun 2011 to Vol.21(6) Jun 2012	14/05/2012 05/07/2012	**34**
International Journal of Sports Medicine	Freely available content via https://www.thieme-connect.de	Title and Abs- Vol.10(1) Feb 1989 to Vol.33(6) Jun 2012	15/05/2012 05/07/2012	**7**
Medicine & Science in Sport & Exercise	University of Chester Subscription via OvidSP	Title and Abs- Vol. 21(1) Feb 1989 to Vol.27(12) Dec 1995 Full Text- Vol.28(10) Jan 1996 to Vol.44(6) Jun 2012	06-12/05/2012 05/07/2012	**192**
Oncology Nursing Forum	University of Chester Subscription via EBSCO host	Title - Vol.16(1) Jan 1989 to Vol.26(10) Dec 1999 Full text- Vol.27(1) Jan 2000 to Vol.38(3) May 2011 Title- Vol.38(4) Jul 2011 to Vol.39(4) June 2012	05-09/05/2012 05/07/2012	**77**
Psycho-Oncology	University of Chester Subscription via EBSCO host	Full text - Vol. 1(1) Apr 1992 to Vol. 20(4) Apr 2011 Title and Abs - Vol. 20(5) May 2011 to Vol. 21(6) Jun 2012	13-14/05/2012 05/07/2012	**74**
Total				**471**

Appendix 13

Assessment of high quality training studies (HQTS) for studies meeting all other inclusion criteria

	Studies considered for inclusion into the review				
	Herrero et al., (2006)	Irwin et al. (2009)	Rahnama et al., (2009)	Saarto et al. (2012)	Winters-Stone et al., (2011)
Aerobic exercise criteria					
• **Frequency** at least three days per week	1	1	0	1	n/a
• **Intensity** 55-85% of max heart rate 40-75% of max heart rate reserve 40-75% of max oxygen uptake reserve	1	1	1	1	n/a
• **Time** 20-60min (min 2 x 10 min contin bouts)	1	1	1	1	n/a
• **Duration of Exercise Intervention** at least six weeks	1	1	1	1	n/a
Aerobic exercise criteria score	**4**	**4**	**3**	**4**	**n/a**
Resistance exercise criteria					
• **Frequency** At least two days per week	1	n/a	1	n/a	1
• **Intensity** to near fatigue at least 60% of one repetition max	1	n/a	1	n/a	1
• **Time** at least 1 set of 10-15 repetitions	1	n/a	1	n/a	1
• **Duration of Exercise Intervention** at least six weeks	1	n/a	1	n/a	1
Resistance exercise criteria score	**4**	**n/a**	**4**	**n/a**	**4**
Overall score / Pass or Fail	**4 (Pass)**	**4 (Pass)**	**3.75 (Pass)**	**4 (Pass)**	**4 (Pass)**

Each exercise intervention was assessed against the four criteria outline in the table above. If the exercise intervention met the criteria 1 point was awarded, if the exercise intervention did not meet the criteria 0 points were awarded. The scores were summed to give an overall HQTS score. For combined aerobic and resistance exercise interventions the training stimulus was assessed for both aerobic and resistance exercise, the scores were summed and the corresponding mean was used to determine HQTS. Studies were classified as HQTS if they scored at three out of four.

Appendix 14

The 25 item CONSORT statement checklist of items that should be reported for a RCT

Item No.	Checklist Item
1a	• Identification as a randomised trial in the title
1b	• Structured summary of trial design, methods, results, and conclusions
2a	• Scientific background and explanation of rationale
2b	• Specific objectives or hypotheses
3a	• Description of trial design (such as parallel, factorial) including allocation ratio
3b	• Important changes to methods after trial commencement (such as eligibility criteria), with reasons
4a	• Eligibility criteria for participants
4b	• Settings and locations where the data were collected
5	• The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
6a	• Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
6b	• Any changes to trial outcomes after the trial commenced, with reasons
7a	• How sample size was determined
7b	• When applicable, explanation of any interim analyses and stopping guidelines
8a	• Method used to generate the random allocation sequence
8b	• Type of randomisation; details of any restriction (such as blocking and block size)
9	• Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
10	• Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
11a	• If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
11b	• If relevant, description of the similarity of interventions
12a	• Statistical methods used to compare groups for primary and secondary outcomes
12b	• Methods for additional analyses, such as subgroup analyses and adjusted analyses
13a	• For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome

Appendix 14: The 25 item CONSORT statement checklist of items that should be reported for RCT /cont.

13b	• For each group, losses and exclusions after randomisation, together with reasons
14a	• Dates defining the periods of recruitment and follow-up
14b	• Why the trial ended or was stopped
15	• A table showing baseline demographic and clinical characteristics for each group
16	• For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
17a	• For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
17b	• For binary outcomes, presentation of both absolute and relative effect sizes is recommended
18	• Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
19	• All important harms or unintended effects in each group
20	• Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
21	• Generalisability (external validity, applicability) of the trial findings
22	• Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
23	• Registration number and name of trial registry
24	• Where the full trial protocol can be accessed, if available
25	• Sources of funding and other support (such as supply of drugs), role of funders

Schulz et al. (2010)

Appendix 15

The Downs and Black Checklist of (1998) methodological quality

Question No.	Reporting	Scoring
1	**Is the hypothesis/aim/objective of the study clearly described?**	Yes = 1 No = 0
2	**Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	**Are the characteristics of the patients included in the study clearly described?** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	**Are the interventions of interest clearly described?** Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	**Are the distributions of principal confounders in each group of subjects to be compared clearly described?** A list of principal confounders is provided.	Yes = 2 Partially = 1 No =0
6	**Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	**Does the study provide estimates of the random variability in the data for the main outcomes?** In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	**Have all important adverse events that may be a consequence of the intervention been reported?** This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	**Have the characteristics of patients lost to follow-up been described?** This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	**Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?**	Yes = 1 No = 0
Reporting Subtotal		***(11)***

Appendix 15: The Downs and Black Checklist of (1998) methodological quality /cont.

Question No.	External validity	Scoring
11	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 UTD = 0
12	**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 UTD = 0
13	**Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?** For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 UTD = 0
External validity Subtotal		***(3)***
	Internal validity – bias	
14	**Was an attempt made to blind study subjects to the intervention they have received?** For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 UTD = 0
15	**Was an attempt made to blind those measuring the main outcomes of the intervention?**	Yes = 1 No = 0 UTD = 0
16	**If any of the results of the study were based on "data dredging", was this made clear?** Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 UTD = 0
17	**In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?** Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 UTD = 0
18	**Were the statistical tests used to assess the main outcomes appropriate?** The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 UTD = 0

Appendix 15: The Downs and Black Checklist of (1998) methodological quality /cont.

Question No.	Internal validity – bias \ cont.	Scoring
19	**Was compliance with the intervention/s reliable?** Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 UTD = 0
20	**Were the main outcome measures used accurate (valid and reliable)?** For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 UTD = 0
Internal validity – bias subtotal		***(6)***
	Internal validity - confounding (selection bias)	
21	**Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?** For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.	Yes = 1 No = 0 UTD = 0
22	**Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?** For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 UTD = 0
23	**Were study subjects randomised to intervention groups?** Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example alternate allocation would score no because it is predictable.	Yes = 1 No = 0 UTD = 0
24	**Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?** All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 UTD = 0
25	**Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?** This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 UTD = 0
26	**Were losses of patients to follow-up taken into account?** If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow up was too small to affect the main findings, the question should be answered yes.	Yes = 1 No = 0 UTD = 0
Internal validity - confounding subtotal		***(6)***

Appendix 15: The Downs and Black Checklist of (1998) methodological quality /cont.

Question No.	Power	Scoring
27	**Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?** Sample sizes have been calculated to detect a difference of x% and y%.	$<n_1$ =0 n_1-n_2 = 1 n_3-n_4 = 2 n_5-n_6 =3 n_7-n_8 =4 n_9+ = 5
Power subtotal		***(5)***
Total		***(32)***

Appendix 16
Downs and Black Checklist (1998) quality scoring for studies included in the review

		Studies included in the review				
Item number Downs and Black (1998) checklist of methodological quality	Maximum score for each item	Herrero et al., (2006)	Irwin et al. (2009)	Rahnama et al., (2009)	Sarrto et al., (2012)	Winters-Stone et al., (2011)
1	1	1	1	1	1	1
2	1	1	1	1	1	1
3	1	1	1	1	1	1
4	1	1	1	1	1	1
5	2	1	2	0	1	2
6	1	1	1	1	1	1
7	1	1	1	1	1	1
8	1	1	0	0	0	1
9	1	0	1	1	1	1
10	1	0	1	1	1	1
Reporting Subtotal	**11**	**8**	**10**	**8**	**10**	**11**
11	1	0	1	1	1	1
12	1	0	0	0	0	0
13	1	1	1	1	1	0
External Validity Subtotal	**3**	**1**	**2**	**2**	**2**	**1**
14	1	0	0	0	0	0
15	1	1	1	1	1	1
16	1	1	1	1	1	1
17	1	1	1	1	1	1
18	1	1	1	1	1	1
19	1	1	1	0	1	0
20	1	1	1	1	1	1
Internal Validity (Bias) Subtotal	**7**	**6**	**6**	**5**	**6**	**5**
21	1	1	1	1	1	1
22	1	1	1	1	1	1
23	1	1	1	1	1	1
24	1	1	1	0	0	1
25	1	1	1	0	1	1
26	1	0	1	0	1	1
Internal Validity (Selection Bias) Subtotal	**6**	**5**	**6**	**3**	**5**	**6**
27	5	5	5	5	5	5
Power Subtotal	**5**	**5**	**5**	**5**	**5**	**5**
Total Score	**32**	**25**	**29**	**23**	**28**	**28**

Appendix 17

Blank data extraction tool

Date of data extraction			
Study Details			
Author			
Year			
Title			
Journal			
Located via			
Accessed from			
Confirm RCT	Yes	No	
Downs and Black Score (32)			
Study characteristics			
Country:			
Sample size:	Controls	Exercisers	
Attrition rate:	Controls	Exercisers	
Population			
Confirm postmenopausal status	Yes	No	
Mean Age (yrs)	Controls	Exercisers	
Body Mass (kg)	Controls	Exercisers	
BMI (kg/m2)	Controls	Exercisers	
Stage of cancer			
Type of treatment			
Type of hormone therapy			
Comparators			
Description			
Intervention			
Confirm HQTS	Yes	No	
Timing in relation to treatment	During Treatment	After Treatment	
Type	Aerobic	Resistance	Mixed
Specific type			
Frequency (times/wk)			
Time			
Intensity			

Appendix 17

Blank data extraction tool /cont.

Intervention					
Duration (wks)					
Setting					
Supervision	Supervised		Unsupervised		
Adherence rate					
Adverse effects					
Outcomes					
Body composition assessment method					
BM (kg)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
BMI (kg/m2)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
FM (kg)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
LBM (kg)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
BF% (%)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
WC (cm)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
BMD (g/cm2)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
BMC (g/cm)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
Notes					

Appendix 18

Example of completed data extraction tool; Herrero et al., (2006)

Date of data extraction	18/06/2012		
Study details			
Author	Herrero, F., San Juan, A. F., Fleck, S. J., Balmer, J., Perez, M., Canete, S. et al.		
Year	2006		
Title	Combined aerobic and resistance training in breast cancer survivors: a randomized, controlled pilot trial		
Journal	International Journal of Sports Medicine		
Located via	MEDLINE, CINHAL, Sports Discus, PEDRO, HS Journal, HS Book		
Accessed from	University of Chester Subscription in Print		
Confirm RCT	Yes	No	
	✓		
Downs and Black Score (32)	**25**		
Study characteristics			
Country:	**Spain**		
Sample size (n)	Controls	Exercisers	
	10	**10**	
Attrition rate (%)	Controls	Exercisers	
	20	**20**	
Population			
Confirm postmenopausal status	Yes	No	
	✓		
Mean Age (yrs)	Controls	Exercisers	
	51 ± 10	**50 ± 5**	
Body Mass (kg)	Controls	Exercisers	
	67.7 ± 8.9	**66.7 ± 10.5**	
BMI (kg/m2)	Controls	Exercisers	
	24 ± 3.2	**25.1 ± 3.5**	
Stage of cancer	**I-II**		
Type of treatment	**SUR + CT + RT**		
Type of hormone therapy	**na**		
Comparators			
Description	**Followed usual sedentary lifestyle (< a total of 30-60min walking, 3x/wk) and no strenuous exercise**		
Intervention			
Confirm HQTS	Yes	No	
	✓		
Timing in relation to treatment	During Treatment	After Treatment	
		✓	
Type	Aerobic	Resistance	Mixed
			✓
Specific type	**Cycle egometer and weight lifting**		
Frequency (times/wk)	**3 combined cycling and weight lifting sessions**		
Time	**Cycling = 20-30 min; weight lifting = 11 ex; 1-2 sets; 8-15 reps**		
Intensity	**Cycling = 70-80% max HR; weight lifting = 8-15 rep max**		

Appendix 18

Example of completed data extraction tool; Herrero et al. (2006) /cont.

Duration (wks)	**8**				
Setting	**Recreational Fitness – community fitness club**				
Supervision	Supervised	Unsupervised			
	✓				
Adherence rate	**91% ± 7%**				
Adverse effects	No major adverse effects and no major health problems				
Outcomes					
Body composition assessment method	**FM and BF% = 3 site skinfold measurement (triceps, abdominal and suprailiac)* Muscle mass = from anthropometrical data****				
BM (kg)	Pre	Post	Change	Difference	P Value
Controls	**67.7**	**67.3**	**-0.4**	**-0.7**	p=>0.05
Exercisers	**66.7**	**65.6**	**-1.1**		
BMI (kg/m2)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
FM (kg)	Pre	Post	Change	Difference	P Value
Controls	**15.3**	**15.3**	**0**	**-1.7**	p=>0.05
Exercisers	**16.4**	**14.7**	**1.7**		
LBM (kg) (muscle mass)	Pre	Post	Change	Difference	P Value
Controls	**28.6**	**28.3**	**-0.3**	1.0	p=<0.05
Exercisers	**27.3**	**28**	**0.7**		
BF% (%)	Pre	Post	Change	Difference	P Value
Controls	**22**	**22**	**0**	**-2.0**	**p=<0.05**
Exercisers	**24**	**22**	**2**		
WC (cm)	Pre	Post	Change	Difference	P Value
Controls					
Exercisers					
BMD (g/cm2)	Pre	Post	Change	Difference	
Controls					
Exercisers					
BMC (g/cm)	Pre	Post	Change	Difference	
Controls					
Exercisers					
Notes					
*** using the equations of Jackson and Pollock (1985) ** using the equations of Lee et al. (2000)**					

Appendix 19

Search location and retrieval of method of studies included in the final review

	Studies included in the review				
Search Location	Herrero et al., (2006)	Irwin et al. (2009)	Rahnama et al., (2009)	Saarto et al., (2012)	Winters-Stone et al., (2011)
MEDLINE	✓	✓	x	x	✓
CINHAL	✓	✓	✓	✓	x
Cochrane Lib	x	✓	x	x	✓
ProQuest	x	x	x	x	x
Sports Discus	✓	✓	x	x	x
Pedro	✓	✓	✓	✓	✓
ZETOC	x	x	x	x	x
SCIRUS	x	x	x	x	x
Hand searched Journals	✓	x	x	x	x
Hand searched Book Chapters	✓	✓	x	x	x
Retrieval method	University of Chester Subscription in Print	Freely Available Via Pubmed Central	Freely Available Via Pubmed Central	British Library via University of Chester Inter-Library Loans	Freely Available Via Pubmed Central

Appendix 20

List of non-English language studies meeting initial eligibility criteria but subsequently excluded from final review on the basis of language

Chae, Y. R., & Choe, M. A. (2001). Effects of exercise on cardiopulmonary functions and shoulder joint functioning in breast cancer patients undergoing radiation therapy after breast cancer [Korean]. Taehan Kanho Hakhoe Chi [Journal of Korean Academy of Nursing], 31(3), 454-466.

Cho, O. H. (2004). Effects of a comprehensive rehabilitation program for mastectomy patients [Korean]. Taehan Kanho Hakhoe Chi [Journal of Korean Academy of Nursing], 34(5), 809-819.

Damm, F. (1996). Sports and breast cancer - exercise, games and sports in breast cancer / Sport and breast cancer: motor activity, leisure time physical activity and playing sports after breast cancer. (Sport und Brustkrebs - Bewegung, Spiel und Sport bei Brustkrebs / Sport et cancer du sein: activite motrice, activite physique de loisir et pratique d'un sport apres un cancer du sein) [German]. Deutsche Zeitschrift fuer Sportmedizin [International Journal of Sports Medicine - German], 47(7/8), 440-441.

de Rezende, L. F., Beletti, P. O., Franco, R. L., Moraes, S. S., & Gurgel, M. S. (2006). Random clinical comparative trial between free and directed exercise in post-operative complications of breast cancer. (Exercicios livres versus direcionados nas complicacoes pos-operatorias de cancer de mama) [Portuguese]. Revista da Associacao Medica Brasileira [Journal of the Medical Association], 52(1), 37-42. doi:10.1590/S01044230200600010020

Appendix 20: List of non-English language studies meeting initial eligibility criteria but subsequently excluded from final review on the basis of language /cont.

Dincer, U., Kaya, E., Cakar, E., Kiralp, M. Z., & Dursun, H. (2007). Effectiveness of comprehensive rehabilitation program and home-based exercise in middle and long term mastectomy related disability (Mastektomiye bagl orta ve gec donem dizabilite tedavisinde kapsaml rehabilitasyon ve ev egzersiz programlar n etkinligi) [Turkish]. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi [Turkish Journal of Physical Medicine and Rehabilitation] 53(4), 138-143.

He, X., Li, H., & Xiang, M. (2006). The effects of comprehensive intervention on quality of life of breast cancer patients [Chinese]. Chinese Journal of Rehabilitation Medicine, (11), 1012-1015.

Latikka, P., Pukkala, E., & Vihko, V. (1997). Exercise and breast cancer (Liikunta ja rintasyöpä) [Finnish]. Duodecim, 113(4), 317-322.

Malicka, I., Pawłowska, K., & Woźniewski, M. (2008). The effect of physical exercises on effort tolerance and work of the trunk muscles in women after breast cancer treatment (Wplyw ćwiczeń fizycznych na zdolność wysiJkową pracę mięśni tulowia kobiet po leczeniu raka piersi) [Polish]. Fizjoterapia [Physiotherapy], 16(3), 48-56.

Appendix 20: List of non-English language studies meeting initial eligibility criteria but subsequently excluded from final review on the basis of language /cont.

Malicka, I., Pawłowska, K., & Woźniewski, M. (2008). The effect of physical exercises on effort tolerance and work of the trunk muscles in women after breast cancer treatment (Wplyw ćwiczeń fizycznych na zdolność wysiJkową i pracę mięśni tulowia kobiet po leczeniu raka piersi) [Polish]. Fizjoterapia [Physiotherapy], 16(3), 48-56.

Moros, M. T., Ruidiaz, M., Caballero, A., Serrano, E., Martnez, V., & Tres, A. (2010). Effects of an exercise training program on the quality of life of women with breast cancer on chemotherapy (Efectos de un programa de entrenamiento físico sobre la calidad de vida de las mujeres con cáncer de mama en la quimioterapi) [Spanish]. Revista Medica de Chile [Chile Medical Journal], 138(6), 715-722.

Park, H. S., Cho, G. Y., & Park, K. Y. (2006). The effects of a rehabilitation program on physical health, physiological indicator and quality of life in breast cancer mastectomy patients [Korean]. Taehan Kanho Hakhoe Chi [Journal of Korean Academy of Nursing], 36(2), 310-320.

Appendix 20: List of non-English language studies meeting initial eligibility criteria but subsequently excluded from final review on the basis of language /cont.

Rezende, L. F., Beletti, P. O., Franco, R. L., Moraes, S. S., & Gurgel, M. S. (2006). Random clinical comparative trial between free and directed exercise in post-operative complications of breast cancer (Ensaio clínico aleatório comparativo entre o exercício livre e dirigido em complicações pós-operatórias de significância de mama) [Portuguese]. Revista da Associação Médica Brasileira [Journal of the Brazilian Medical Association], (1), 37-42.

So, H. S., Kim, I. S., Yoon, J. H., & Park, O. J. (2006). Effects of aerobic exercise using a flex-band on physical functions & body image in women undergoing radiation therapy after a mastectomy [Korean]. Taehan Kanho Hakhoe Chi [Journal of Korean Academy of Nursing], 36(7), 1111-1122.

The Norwegian Knowledge Centre for the Health, S. (2009). Rehabilitation of breast cancer patients (Rehabilitering av brystkreftpasienter) [Norwegian]. Oslo: Den norske kunnskapssenter for helsetjenesten [Oslo: The Norwegian Knowledge Centre for the Health Services].

Wang, B. G., Yuan, X. Y., Wang, Q. T., Luan, X. D., Wang, C. P., Jia, A. L., . . . Sun, Y. (2005). Functional rehabilitation gymnastics for the edema of upper limbs and the activity of shoulder joint in postoperative patients with breast cancer [Chinese]. Zhongguo Linchuang Kangfu [Chinese Journal of Clinical Rehabilitation], 9(30), 16-19.